cancers

Review

Fascin in Gynecological Cancers: An Update of the Literature

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Simple Summary: Fascin, an actin-binding protein, is upregulated in different types of human cancers. It is reportedly responsible for increasing the invasive and metastatic ability of cancer cells by reducing cell–cell adhesions. This review provides a brief overview of fascin and its interactions with other genes and oncoviruses to induce the onset and progression of cancer.

Abstract: Fascin is an actin-binding protein that is encoded by the *FSCN1* gene (located on chromosome 7). It triggers membrane projections and stimulates cell motility in cancer cells. Fascin overexpression has been described in different types of human cancers in which its expression correlated with tumor growth, migration, invasion, and metastasis. Moreover, overexpression of fascin was found in oncovirus-infected cells, such as human papillomaviruses (HPVs) and Epstein-Barr virus (EBV), disrupting the cell–cell adhesion and enhancing cancer progression. Based on these findings, several studies reported fascin as a potential biomarker and a therapeutic target in various cancers. This review provides a brief overview of the FSCN1 role in various cancers with emphasis on gynecological malignancies. We also discuss fascin interactions with other genes and oncoviruses through which it might induce cancer development and progression.

Keywords: fascin; gynecological cancer; ovarian cancer; cervical cancer; biomarker

1. Introduction

Fascin, also known as *fascin-1* (*FSCN1*) or actin-bundling protein-1, is a globular filamentous actin-binding protein belonging to the actin cytoskeletal protein family [1]. Molecular cloning techniques showed fascin to be highly conserved during the course of evolution. Furthermore, fascin is homologous to several species, including the Drosophila singed gene [2], Xenopus [3], and mouse [4]. *FSCN1* plays a crucial role in the assembly and maintenance of various cellular structures, including filopodia, stress fibers, lamellipodia, invadopodia, dendrites, and spiky protrusions underlying the plasma membrane [5–8]. In addition to its role in maintaining actin structure, *FSCN1* regulates several cellular physiological processes, including cell-to-cell interactions, cell-to-matrix adhesion, cell motility, cell migration and invasion as well as focal adhesion dynamics, histone methylation, and gene transcription [9–13].

There are three isoforms of *FSCN* (*FSCN1*, *FSCN2*, and *FSCN3*) present in humans as well as other vertebrates. Of the three isoforms, *FSCN1* is expressed during development in the mesenchymal and nervous tissues and is the most extensively studied form of fascin [14]. On the other hand, *FSCN2* is expressed in hair and retinal cells [15,16], while *FSCN3* is present in the testis and developing spermatozoa [17]. Both *FSCN-2* and *-3* are homologous to *FSCN-1* by 56% and 29%, respectively.

While in normal tissues there is low or lack of *FSCN1* expression, in transformed epithelial cells and carcinomas, it is highly expressed [18]. In different cancers, including colon, pancreatic, breast, lung, esophagus, stomach, skin, and ovarian cancers, elevated

expression of *FSCN1* is associated with increased metastatic potential and poor prognosis, indicating its role as a candidate potential biomarker and therapeutic target [19]. Here we discuss the current knowledge of *FSCN1* and its underlying mechanisms in order to elucidate its multiple roles in the onset and progression of gynecological cancer.

2. Structure of Fascin

In humans, the *FSCN1* (Gene ID: 6624) encodes a distinct 493 amino acid polypeptide and is located on the short arm of chromosome 7, encompassing ~14 kb of DNA including 5 exons.

X-ray crystal structure and sequence analyses revealed *FSCN1* to consist of four tandem β-trefoil domains (residues 8–139, 140–260, 261–381, and 382–493) organized as two twisted lobes (β-trefoil 1 and 2; β-trefoil 3 and 4), each of which includes six 2-stranded β-hairpins [20]. Studies demonstrated that all the four β-trefoil domains of *FSCN1* play a role in actin binding; while the actin-binding site (ABS)-1 involves the β-trefoil 1 and 4, ABS-2 includes residues from β-trefoil 1 and 2, and ABS-3 involves β-trefoil 3 [21]. Microtubules interact with *FSCN1* directly via β-trefoil 2, plausibly inhibiting ABS-1 [12]. The ABS-1 region is located in the first beta-trefoil domain between amino acids 33–47 and consists of a highly conserved site (Ser39) in the center of ABS-1, which can be phosphorylated by protein kinase C (PKC); studies have indicated Ser39 phosphorylation inhibits *FSCN1* activity [22,23]. In addition to Ser39, *FSCN1* consists of another phosphorylation site, Ser274; mutation of Ser274 to alanine is also involved in inhibiting fascin-bundling activity; however, Ser274 does not lie in the region of ABS1-3 [21,24,25]. On the other hand, ABS-2 consists of two lysine residues (K247/K250) located at the lysine-rich loop at the β-trefoil domain 2 of *FSCN1* (between amino acids 241–250) [26]; monoubiquitylation of *FSCN1* at K247/K250 stimulates bundle assembly [27]. The postulated location for the other ABS is between amino acids 277–493 [10].

3. Functions of Fascin

Physiologically, *FSCN1* is expressed at comparatively low levels in normal cells as compared to malignant cells. Therefore, the distinct roles of *FSCN1* in both cell types are important to review.

3.1. Function of Fascin in Normal Cells

As mentioned in the section above, *FSCN1* is an actin-bundling protein and crosslinks actin filaments via the three binding sites [5,7,21]. *FSCN1* plays a role in the formation and stabilization of several cellular protrusions (microspikes, lamellipodia, and filopodia) [5,7,21] which are essential for cell-to-cell adhesion, cellular interaction, motility, and migration [9–11]. Additionally, *FSCN1* also regulates focal adhesion dynamics in multiples types of cells and is partially dependent on the canonical actin-bundling function of *FSCN1* [6,12]. Moreover, during normal development, *FSCN1* controls cellular processes including cell migration, neurite cone extension, and dendrite formation [19,28,29]. During dendritic cell maturation, *FSCN1* is highly expressed; *FSCN1*-dendritic cells aid in effectual interaction and present antigens to T cells, thus playing a vital role in adaptive and innate immunity [30].

On the other hand, *FSCN1* binds to microtubule cytoskeleton and regulates focal adhesion dynamics and cell migration [12]. Interruption in *FSCN1* and microtubule interaction leads to stability of cell adhesion and reduces cell migration [12]. During cell migration and invasion, *FSCN1* interacts with nesprin-2, a nuclear envelope protein to promote nuclear deformation and mobility [31]. Nevertheless, the phosphorylated form of *FSCN1* is present in the nucleus and controls histone methylation and gene transcription by interaction with H3K4me3, the H3K4 methyltransferase core subunit RbBP5 form [13]. Nonetheless, *FSCN1* regulates extracellular vesicle release [32].

FSCN1 is expressed during mouse embryonic development; however, its expression patterns are widely conserved in human tissues [14,28]. In Drosophila oogenesis, *FSCN1*

also plays an important role in delamination during border cell migration by modifying the localization of E-cadherin in the border cells [33]. During embryogenesis, as compared to adults, *FSCN1* is significantly expressed during development. In adults, *FSCN1* is absent or at low levels in normal epithelial cells, and its expression is limited to the neuronal, endothelial, mesenchymal, dendritic, and immune cells [18]. During embryogenesis, *FSCN1* is largely expressed in the nervous systems (neuroblasts, melanoblasts, mesenchymal tissue, microcapillary endothelial cells, and antigen-presenting dendritic cells) [18,34,35].

3.2. Function of Fascin in Cancer Cells

When epithelial cells undergo the transformation, *FSCN1* expression levels are highly elevated [36]. *FSCN1* overexpression is documented in the majority of cancers, including ovarian [37], breast [38], colon [39], pancreatic [40,41], glioma [42], melanoma [43], leukemia [44], lymphoma [45], and esophageal squamous cell carcinoma [46]; however, the underlying molecular mechanisms of *FSCN1* activation during the onset and progression of cancer are still understated. Although mutations or amplification of *FSCN1* gene are not common, hypomethylation of *FSCN1* promoter has been found in normal epithelium and cancer cells alike [46], indicating the lack of epigenetic aberration of *FSCN1* in cancer.

The role of *FSCN1* in cancer was first described in breast cancer by Grothey et al. [47], where the authors showed that overexpression of *FSCN1* induced aggressive phenotype. Several additional investigations also reported the role of *FSCN1* in other types of cancer and its association with an aggressive phenotype, poor prognosis, and short survival [19,36,48,49]. An earlier study found significant overexpression of FSCN1 in human epithelial tumors (lung, cervical, ovarian, esophageal, pancreatic, gastric, hepatocellular, colorectal, breast, nasopharyngeal, and laryngeal carcinomas) in comparison with their corresponding normal tissues, leading to the conclusion that overexpression of FSCN1 correlates with tumor occurrence and progression [50]. In this regard, it was found that *FSCN1* can promote cancer progression through both canonical and non-canonical pathways by triggering cancer proliferation, migration, invasion, and metastasis [19,36].

There are several functions by which *FSCN1* promotes cancer progression via inducing cancer cell growth, proliferation, migration, invasion, and metastasis [19,36]. In vitro findings reported contrasting roles of *FSCN1* in cell growth and proliferation. While upregulated expression of *FSCN1* was found to be correlated with enhanced cell proliferation in different cancer cell lines [51–53], few studies reported no significant cell proliferation in *FSCN1*-transduced cancer cells [54,55]. While one study in the aggressive breast cancer cell line, MDA-MB-231, reported stimulated *FSCN1* expression to provoke cell proliferation [51], other investigations by Al-Alwan et al. [56] and Heinz et al. [57] did not report a significant effect of transduced *FSCN1* expression on MDA-MB-231 cell proliferation. Similarly, in the non-small lung cancer cell line, A549, it was reported that enhanced *FSCN1* has a light impact on cell proliferation [58]; however, another study using A549 cells reported that *FSCN1* could enhance cell proliferation via the YAP/TEAD signaling pathway [52]. Moreover, knockdown of *FSCN1* leads to the inhibition of the A549 cell growth and proliferation via the MAPK signaling pathway [59].

On the other hand, one of the principal functions of *FSCN1* contributions to cancer progression is the actin-bundling function [6]. Alterations in the dynamics of microtubules, including their expression and stability, have been shown to lead to cancer invasion and metastasis [57,60]. *FSCN1* also facilitates mechano-transduction by interaction with the LINC complex, which is responsible for cell invasion and migration [31,61,62]. The other function includes the role of *FSCN1* within the nucleus to control nucleolar size and morphology [63], in addition to nuclear actin [64,65], chromatin regulation, and assembly [13]. Thus, deregulation in these functions contributes to cancer development and progression [65–67]. Additionally, *FSCN1* also regulates oxidative phosphorylation of the mitochondria and metabolic stress resistance, thus inducing cancer metastasis [54].

Moreover, in vitro data also demonstrated the role of *FSCN1* in inducing cancer cell migration by promoting filopodia formation and epithelial-mesenchymal transition

(EMT) [68] in various cancer cells, including ovarian [37], oral [53], hypopharyngeal [69], osteosarcoma [70], and pancreatic cancer cells [41]. *FSCN1* induces filopodia and invadopodia stability and formation [7]. In addition, it enhances the expression of matrix metalloproteinases (MMPs) [41,69], thus promoting cancer cell motility and invasion. On the other hand, in vivo studies using different models also reported *FSCN1*-induced migration and invasion. In mouse and zebrafish models, *FSCN1* expression was found to induce colon tumor invasion [71,72]. Similarly, breast cancer in vivo models reported elevated *FSCN1* expression to induce cancer cell metastasis to the lung [40]. In nude mice models, overexpression of *FSCN1* was linked with metastasis in pancreatic [73], renal [74], and colorectal carcinomas [75]. Additionally, in severe combined immunodeficiency (SCID) mice, enhanced *FSCN1* expression provoked lung metastasis in osteosarcoma cells [70]. Furthermore, previous studies reported that *FSCN1* could promote cancer progression by inducing chemoresistance in cancer cells as well as controlling metabolism and contributing to a de-differentiated and more stem-like state [76].

3.3. Mechanisms of Fascin Deregulation

Numerous transcriptional factors (TFs) interact and bind to the *FSCN1* promoter regions, thus regulating *FSCN1* expression. It was reported that *FSCN1* transcriptional activity is controlled by the promoter region ($-219/+114$); in breast and colon cancer, CREB and aryl hydrocarbon receptors (AhRs) bind with the $-219/+114$ promoter region [77]. On the other hand, in human oral cancer, Lee et al. [78] reported that interleukin (IL)-1β triggered phosphorylation of several key players, including CREB, ERK1/2, JNK, and NF-κB, thereby inducing *FSCN1* expression and promoting invasion (Figure 1). Furthermore, cytokines (IL-6 or tumor necrosis factor-alpha (TNF-α) trigger the NF-κB and STAT3 pathways, which are essential for enhancing *FSCN1* expression in cancer [79–81] (Figure 1). In gastric cancer, one study reported that Fas signaling induces *FSCN1* expression via the STAT3 pathway [82]; another study demonstrated that galectin-3 regulates the GSK-3β/β-catenin/TCF-4 signaling pathway, thus triggering *FSCN1* expression [83] (Figure 1). In colorectal cancer, the β-catenin-TCF signaling pathway was reported to regulate *FSCN1* transcription [84]; however, the studies in breast and colon cancer failed to report the regulation of *FSCN1* expression via β-catenin-TCF signaling [77,85]. Another study in colorectal cancer demonstrated loss of p53 to induce *FSCN1* expression via the NF-κB pathway [86] (Figure 1). Moreover, in esophageal squamous cell carcinoma, overexpression of the epidermal growth factor (EGF) increased specificity of protein 1 (Sp1) phosphorylation and activated the ERK1/2 pathway, thus enhancing *FSCN1* expression [87] (Figure 1). Furthermore, the snail family of transcription factors was reported to be involved in *FSCN1* transcription; SNAIL2 expression induced *FSCN1* expression in human colon and pancreatic cells [40]. In head and neck cancer cells, SNAIL2 was found to directly bind to the *FSCN1* promoter, inducing *FSCN1* expression (Figure 1) [88]. On the other hand, in hypopharyngeal and pancreatic cancers, HIF-1α was reported to induce the overexpression of *FSCN1* [41,69] (Figure 1). Nevertheless, a study by Megrioni and colleagues [89] demonstrated the overexpression of *FSCN1* in NT2 cells, known to be deficient of the CREB-binding protein during neurogenesis, indicating a viral role of *FSCN1* in the formation of mature neurons (Figure 1).

Similar to transcription factors regulating *FSCN1* expression, microRNAs (miRNAs) are known to bind to the 3′ untranslated region (UTR) of *FSCN1* and regulate its expression in several human cancer tissues and cell lines, including breast, lung, liver, colon, cervix, prostate, pancreatic, hepatocellular, esophageal, and nasopharyngeal [90–101]. On the other hand, loss of miRNAs -133a and -145 was found to enhance *FSCN1* expression, thus stimulating cancer cell growth, proliferation, migration, and invasion along with the inhibition of apoptosis [90–94,96–101]. In addition, *FSCN1* is directly targeted by several miRNAs in different cancers. Thus, miRNA-24 targets *FSCN1* in nasopharyngeal and prostate cancer [95,102], *FSCN1* is targeted by miRNA-143 in esophageal [103] and miRNA-326 in lung and gastric cancers [104,105], respectively. Yu et al. demonstrated that the

loss of miRNA-663 in colorectal cancer cells induced *FSCN1* expression [106]. Chen et al. reported overexpression of miRNA-451 to enhance *FSCN1* expression via the inhibition of AMPK and activation of mTOR signaling [107].
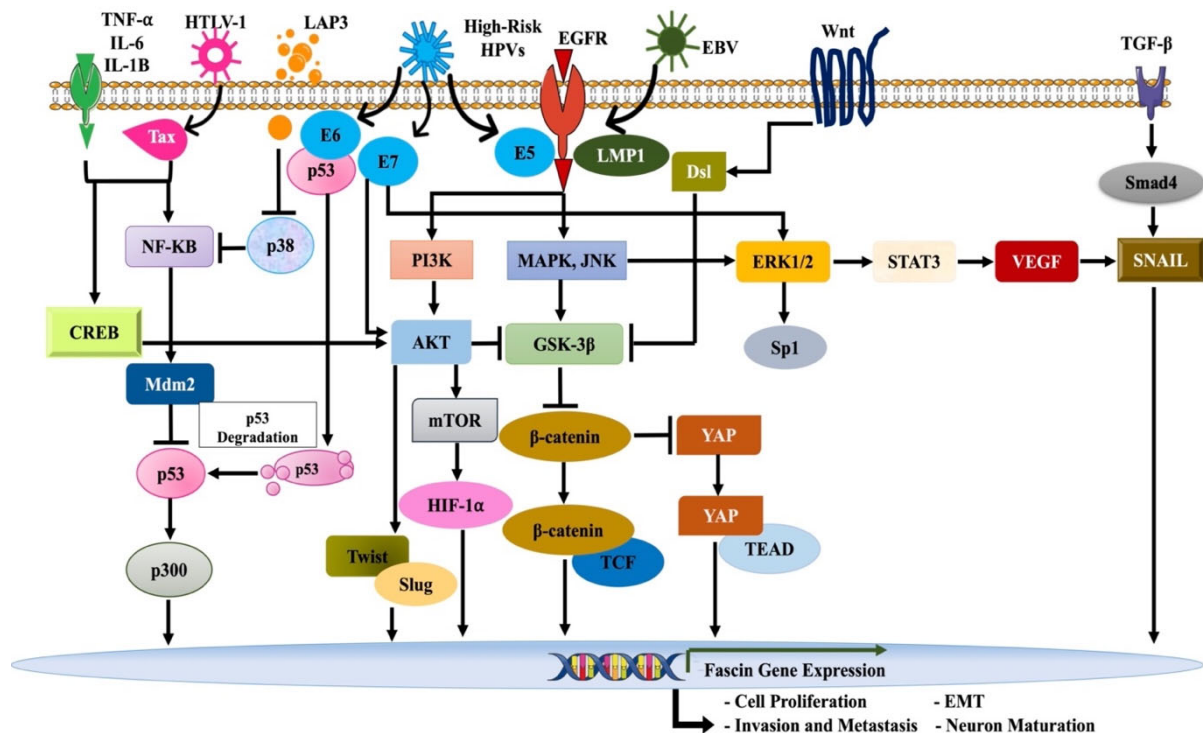

Figure 1. Mechanisms of *FSCN1* deregulation. Several factors, including EGFR, TGF-β, and interleukins, in addition to oncoviruses, trigger key pathways including CREB, ERK1/2, JNK, STAT3, PI3K, MAPK, and NF-κB to deregulate *FSCN1* expression and stimulate underlying mechanisms for cancer progression.

3.4. Role of Oncoviruses in Fascin Deregulation

Previous studies have shown potential deregulation of *FSCN1* via viral oncogenesis (Figure 1). In this regard, overexpression of *FSCN1* was reported in Epstein-Barr virus (EBV)-induced lymphoblastoid cell lines [108]. More specifically, LMP1, one of the onco-proteins of the EBV, was found to stimulate *FSCN1* in lymphocytes via NF-κB signaling, contributing to lymphocyte migration and invasion [44]. While *FSCN1*-negative Hodgkin's lymphoma-derived cell lines also show upregulated *FSCN1* levels [44], LMP1-negative Burkitt lymphoma-derived cell lines are negative for *FSCN1* expression [109]. Moreover, a study by Liu et al. in EBV-positive nasopharyngeal carcinoma reported that enhanced LMP1 levels and phosphorylated STAT3 elevated *FSCN1* expression and was associated with lymph node metastasis and higher proliferation index of the cancer cells [110]. Since LMP1 is present in epithelial cells and is known to have a potential role in EBV production [111], continuous expression of *FSCN1* can help in EBV release. Moreover, the transmission of EBV to epithelial cells is dependent on NF-κB signaling [112], which is one of the major factors for effective *FSCN1* induction. LMP1 of EBV can induce expression of *FSCN1* at both mRNA and protein levels in lymphocytes [113]. Studies by Mohr et al. [44,113] demonstrated that the inhibition of NF-κB signaling using a chemical inhibitor of IκB kinase β (IKKβ) or cotransfection of a dominant-negative inhibitor of IκBα (NFKBIA) decreased both *FSCN1* levels and the invasive ability of EBV-transformed lymphoblastoid cells. Moreover, the study showed that the knockdown of *FSCN1* by two different small hairpin RNAs reduced invasion of lymphocytes [113]. Similarly, in LMP1-positive Jurkat T lymphocytes, *FSCN1* is reported to induce cell migration [114]. In colorectal cancer, upregulated *FSCN1* expression was reported in LMP1-positive samples and was associated

with moderately to poorly differentiated adenocarcinomas [115]. The study suggested that Wnt/β-catenin signaling regulates epithelial-mesenchymal transition (EMT) induced by *FSCN1* in LMP1-positive cancers to provoke cancer progression (Figure 1) [115]. Likewise, in EBV-associated gastric cancer, upregulated Smad4/FSCN1 expression significantly correlated with larger tumor size, higher histological grade, lymph node involvement, vascular invasion, and poor clinical outcome [116].

FSCN1 upregulation was also correlated with other oncoviruses. Kress et al. [117] reported that Tax, the oncoprotein of leukemia-inducing retrovirus HTLV-1, could upregulate *FSCN1* expression through the regulation of the NF-κB signaling pathway (Figure 1). A recent study in adult T-cell leukemia/lymphoma (ATLL) with HTLV-1–infected Hodgkin and Reed-Sternberg–like cells found elevated *FSCN1* expression [118]. Gross and colleagues [119] further found *FSCN1* to play a vital role in the transport of viral proteins to budding sites and promote HTLV-1 transmission.

FSCN1 was also reported to be associated with high-risk HPV to enhance cancer progression. It is well-known that high-risk HPVs are major players in the onset and progression of cervical cancer and correlate with lymph node and vascular invasion and the tumor size [120,121]. More specifically, Yasmeen et al. [122] investigated the expression of oncogenes, including *FSCN1*, in cervical cancer. In this study, the use of Src/Abl inhibitor in HPV-positive cervical cancer cell lines (SiHa and HeLa) was found to restore β-catenin accompanied by the downregulation of *FSCN1* expression pattern, thus inhibiting cell invasion ability of these cancer cell lines [122]. In addition, a study in Iran was carried out to investigate the prevalence of HPV and *FSCN1* in cervical squamous cell carcinoma and found an association between *FSCN1* overexpression and HPV positivity [123]. The association of HPV with *FSCN1* was also reported by our group [124], where we demonstrated that E6/E7 oncoproteins of HPV is associated with *FSCN1* overexpression in human colorectal cancer. These studies clearly show that human oncoviruses can deregulate the expression patterns of *FSCN1*, thereby promoting cancer progression (Figure 1).

4. Fascin in Gynecological Cancers

Numerous studies have reported overexpression of *FSCN1* in various gynecological cancers [123,125–147] as indicated in Table 1.

Table 1. Fascin Overexpression in Gynecological Cancers and its Association with Clinico-pathological Features.

Type of Cancer	Detection Method (Assay)	Clinicopathological Features	References
Ovarian Cancer	IHC	Poor overall survival and prognosis	[127]
	IHC	Serous subtype, micropapillary pattern, FIGO stage, and risk of recurrence	[128]
	IHC	Serous subtype and residual postoperative tumor	[130]
	ICC and IHC	Involved with intraperitoneal invasion	[131]
	IHC	Presence of vascular invasion, psammomatous calcifications, and lymphocytic infiltration	[132]
	IHC	-	[134]
	IHC and WB	Tumor aggressiveness	[137]
	IHC	-	[125]
	IHC	-	[126]
	IHC	T and Nstage, AJCC clinical stage, and poor survival rate	[138]
	IHC	Advanced TNM stage, poor histological differentiation, and poor survival rate	[139]
	IHC and IF	Invasion and migration, metastasis, colonization, and poor prognosis	[140]
	IHC	Tumor grade and tumor aggressiveness	[147]

Table 1. *Cont.*

Type of Cancer	Detection Method (Assay)	Clinicopathological Features	References
Endometrial Cancer	IHC	Tumor grade and neural invasion	[129]
	IHC	High tumor grade	[133]
	IHC	Tumor aggressiveness, distant metastasis, and local recurrence	[141]
	IHC	Lymphovascular space invasion and epithelial-mesenchymal transition	[143]
	IHC	Higher expression in leiomyosarcoma	[135]
	IHC	Extrapelvic disease, higher stage, larger tumor size, shorter progression-free interval, and reduced ER-α expression	[142]
Vulvar Cancer	IHC	-	[145]
Cervical Cancer	IHC	Increased invasivion	[136]
	IHC	Tumor invasion	[144]
	NM-PCR and IHC	HPV overexpression	[123]

ICC: immunocytochemistry; IF: immunofluorescence; IHC: immunohistochemistry; NM-PCR: nested multiplex polymerase chain reaction; WB: Western blot.

4.1. Fascin in Ovarian Cancer: A Candidate Biomarker and Potential Therapeutic Target

A previous report revealed higher FSCN1 expression in borderline and malignant ovarian tumors as compared to benign cases; however, no significant difference was reported between FSCN1 staining in borderline and malignant cases [147]. In contrast, another investigation reported enhanced expression of FSCN1 in primary, borderline, and metastatic ovarian cancers compared with the normal ovarian tissues where no FSCN1 expression was observed. The authors found that FSCN1 expression was associated with the increased risk of intraperitoneal tumor growth and spread [131]. In addition, the authors detected elevated FSCN1 expression in cell cultures derived from patients with stage IV ovarian cancer compared with cell cultures derived from stage II-III ovarian cancer patients [131]. In another study, Daponte et al. [127] showed FSCN1 expression in advanced poorly differentiated serous ovarian cancer that was associated with poor prognosis, suggesting FSCN1 as an independent prognostic biomarker. More interestingly, an IHC analysis using TMAs to analyze the expression of six EMT biomarkers (FSCN1, cortactin, survivin, EGFR, MMP-2, and MMP-9) in serous carcinomas, mucinous carcinomas, endometrioid adenocarcinomas, and clear cell carcinomas found significant expression of only FSCN1, cortactin, survivin, and EGFR [138]. The study also reported higher scoring for FSCN1 in mucinous carcinomas, which was associated with TNM stage and poorer survival rate [138]. Another study also reported upregulated expression of FSCN1, cortactin, and EGFR in TMAs of four ovarian carcinomas (serous carcinoma, mucinous carcinoma, endometrioid adenocarcinoma, and clear cell carcinoma) [139]. Moreover, FSCN1 overexpression was associated with advanced cancer stage, poorer histological differentiation, and survival rate of mucinous carcinoma, suggesting a potential role of FSCN1 as a candidate biomarker for aggressive serous and mucinous carcinomas [139]. On the other hand, previous studies also reported overexpression of FSCN1 in epithelial ovarian cancer and indicated the interaction between cell and matrix as a vital step in the progression of malignant epithelial ovarian neoplasms [130,134]. Moreover, high FSCN1 scoring was associated with poorer tumor differentiation in serous, mucinous, and endometrioid adenocarcinoma, indicating a role of FSCN1 in analyzing tumor aggressiveness, and was suggested as an independent prognostic risk factor in mucinous carcinoma [138]. Similarly, Coa et al. [126] revealed enhanced expression of FSCN1 in primary mucinous carcinomas in comparison with borderline mucinous tumors with a significant expression in metastatic tumors as compared with primary tumors. Furthermore, while FSCN1 expression was significantly upregulated in

borderline and malignant ovarian tumors, there was no expression of FSCN1 in benign ovarian tumors [125]. Another immunohistochemical study revealed that a strong FSCN1 positivity was associated with serous subtype and micropapillary growth pattern [128]. Another investigation by Kostopoulou et al. [137] analyzed the expression of FSCN1 in ovarian cancer using IHC and Western blotting and reported an upregulation of FSCN1 expression in invasive ovarian carcinomas as compared with borderline tumors and cystadenomas. In addition, the study pointed out an association between FSCN1 overexpression and advanced stage and aggressive phenotype [137]. Thus, evaluating FSCN1 expression as a biomarker depicting the progression and outcomes of several types of gynecological cancers has been the center of renewed interest. Another investigation found significantly higher stromal FSCN1 expression in borderline and malignant epithelial ovarian tumors in comparison to normal ovaries and benign epithelial ovarian tumors [132].

McGuire and colleagues showed that the silencing of FSCN1 in ovarian cell lines (HeyA8, Ovcar5, and Tyk-nu), primary human cancer-associated fibroblasts and primary human omental mesothelial cells reduced metastasis [140]. TMA analysis showed higher FSCN1 expression in the tumor stroma than in cancer compartments, and this was associated with the advanced tumor stage [140]. In vitro and in vivo data showed that the loss of FSCN1 significantly inhibited trans-mesothelial migration of the ovarian cancer cell line ES-2 and reduced the interaction between ovarian cancer cells and mesothelial cells in the mouse peritoneal cavity [148]. Moreover, overexpression of FSCN1 in SKOV3 (ovarian cancer cell line) triggered trans-mesothelial migration [148]. On the other hand, in mature and immature neural components, the expression of FSCN1 was detected regardless of rosette formation in immature teratomas derived from both human ovary stem cells, indicating FSCN1 immunostaining as a potential biomarker in diagnosing and grading human immature teratomas [146].

A recent study examined the effect of curcumin against FSCN1 in the ovarian cancer cell line SKOV3 and found curcumin to inhibit STAT3 via the JAK/STAT3 signaling pathway. Notably, the inhibition of STAT3 also led to FSCN1 activity inhibition [149]. In addition to blocking FSCN1, in curcumin-exposed ovarian cancer cells, the formation of filopodia was disrupted, and cell migration was reduced [149]. Recently, Yoshihara et al. [148] documented the importance of filopodia in the trans-mesothelial migration of ovarian cancer cells. Additionally, in athymic nude mice, FSCN1 activity was inhibited therapeutically with the compound G2 [140]. The treatment inhibited the actin-bundling into stress fibers as well as ovarian cancer cell migration by reducing GTP-bound Cdc42 and Rac1, further indicating a therapeutic role of G2 in ovarian cancer [140,150].

4.2. Fascin in Endometrial Cancer: A Potential Biomarker and Therapeutic Target

Similar to ovarian cancer, studies were performed to detect FSCN1 expression in uterine cancer. Uterine carcinosarcoma cases were assessed for FSCN1 expression using IHC; while FSCN1 was absent in benign cases, it was present in both malignant epithelial and mesenchymal elements of uterine carcinosarcomas. This finding was associated with a more aggressive phenotype (advanced stage and large tumor size) and a poor outcome [142]. Additionally, FSCN1 was found to be a potential IHC biomarker in differentiating uterine leiomyosarcoma from leiomyoma [135]. In undifferentiated endometrial carcinomas, the studies reported a loss of E-cadherin and β-catenin and overexpression of FSCN1, galactin-3, cyclin D1, and p16, which is involved in EMT and invasion, thus contributing to aggressive behavior and poor prognosis [141,143,151]. Another investigation revealed significant overexpression of FSCN1 in proliferative endometrial carcinoma samples as compared with the control samples with a significant association with tumor grade and neural invasion [129]. In another report, Kabukcuoglu et al. [133] showed that during endometrial neoplasia development, there was a loss of stromal FSCN1 expression and its increase in the epithelial compartment; this finding was associated with tumor grade and overall survival. The overexpression of FSCN1 protein was also reported in

vulvar cancer; however, immunostaining failed to distinguish in situ from invasive lesions as well as putative HPV-associated and HPV-independent squamous cell carcinomas [145].

4.3. Fascin in Cervical Cancer: A Potential Biomarker and Therapeutic Target

In spite of the confirmed role of FSCN1 in several human carcinomas, there has been a limited number of investigations pertaining to the presence and role of FSCN1 in cervical cancers. In this context, Stewart et al. analyzed FSCN1 expression by IHC in in situ and invasive adenocarcinoma of the endocervix and found FSCN1 overexpression to occur during the development and progression of some endocervical neoplasms, indicating the role of FSCN1 in tumor invasion [144]. Koay et al. [136] reported the expression pattern of FSCN1 in cervical carcinoma by IHC; the normal endocervical epithelium was negative for FSCN1, while the normal squamous epithelial stained positive for FSCN1 in basal and parabasal cells [136]. Furthermore, cervical endothelial cells had constant FSCN1 staining, whereas, in CIN lesions and invasive squamous cell carcinomas, there was high FSCN1 expression [136]. Both studies indicate FSCN1-induced invasion in cancer cells due to loss of cell-to-matrix adhesion [132,136]. In addition, in our laboratory, we found FSCN1 to be overexpressed in cervical cancer tissue (Figure 2).
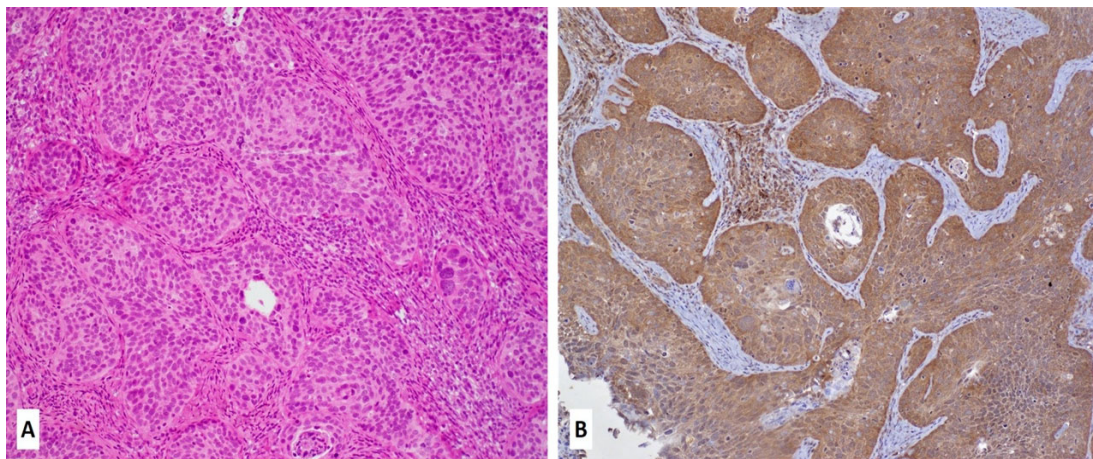

Figure 2. Fascin expression in cervical cancer (**A**,**B**). A case of invasive squamous cell carcinoma of the uterine cervix: (**A**) hematoxylin and eosin slide (20×) with diffused and strong immunohistochemical expression of the fascin protein in cancer cells (**B**, 20×).

5. Fascin in Other Cancers

Several previous studies analyzed *FSCN1* expression using PCR and immunohistochemistry (IHC), revealing its increased expression compared to normal tissues. A systematic review and meta-analysis of studies analyzing the relevance of *FSCN1* in five different carcinomas (breast, colorectal, esophageal, gastric, and lung) by IHC reported that FSCN1 correlates with a high risk of disease progression in breast and colorectal cancers [48]. They also noted that FSCN1 expression is associated with a high risk of mortality in breast, colorectal, and esophageal cancers. Moreover, FSCN1 expression is linked with a high risk of distant and lymph node metastasis in colorectal and gastric carcinomas [48].

Of the gastrointestinal cancers, esophageal cancers has the worst prognosis. FSCN1 is involved in the pathogenesis and metastasis of esophageal carcinoma; high FSCN1 expression increases gradually from the normal to the invasive form and correlates with cell proliferation, lymph node invasion, metastasis, and high tumor stage [152–156]. Moreover, overexpression of FSCN1is associated with poor overall and disease-free survival [155]. On the other hand, gastric carcinoma studies using TMA and IHC reported FSCN1 overexpression at both mRNA and protein levels [157,158]; high FSCN1 expression is associated with tumor size, poorly differentiated tumors, invasion, metastasis, TNM stage, and poor

survival [157,159–163]. In the colon as well, FSCN1 expression is higher in sporadic and familial colorectal adenomas and adenocarcinomas as compared to the healthy colon [164]; FSCN1 expression was reported to progress from focal during the early stages to diffused in the advanced stages [165]. Increased FSCN1 expression is associated with poor clinico-pathological outcomes including advanced tumor stage, grade, and lymph node invasion with poor overall survival and disease-free survival rates [48,166,167]. Therefore, FSCN1 is suggested as a poor prognostic marker for regional and distant metastasis [167,168]. More-over, FSCN1 expression is also reported in K-ras mutant tumors [169]. FSCN1 expression is also higher in hepatocellular carcinoma tissues compared with normal liver tissues which significantly correlates with the tumor grade, lymph node invasion, and distant metastasis in addition to poor prognosis [170–172]. However, a study by Lin et al. showed no corre-lation between FSCN1 overexpression and clinicopathological features [171]. Similar to all gastrointestinal cancers, in pancreatic cancer, there is an increase in FSCN1 expression during carcinogenesis progression (from pancreatic intraepithelial neoplasia to pancreatic adenocarcinoma); high FSCN1 expression correlates with higher histological grades, and poor overall survival [40,41,173].

While lymphocytes, myeloid, and plasma cells stain negative for FSCN1, in human hematologic malignancies including HIV-related lymphoid hyperplasia, Reed-Sternberg cells, Hodgkin's lymphoma, Castleman's disease, and other lymphoid hyperplasia, FSCN1 is overexpressed [174,175]. A study by El Kramani et al. [176] determined FSCN1 levels in with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) cases in comparison to controls using enzyme-linked immunosorbent assay in the plasma and leukocytes and found FSCN1 expression significantly elevated in AML but not in ALL cases, suggesting FSCN1 as a potential biomarker for AML. Another study analyzed differential expression of FSCN1 in classic Hodgkin lymphoma (CHL), anaplastic large cell lymphoma (ALCL), and diffused large B-cell lymphoma (DLBCL); the study showed that FSCN1 is significantly upregulated in CHL as compared to DLBCL and ALCL, indicating a role of FSCN1 in the differential diagnosis of CHL against ALCL and DLBCL [177].

6. Therapeutic Potential of Fascin

Due to the ability of *FSCN1* to induce cell migration, invasion, and metastasis, *FSCN1* is a potential candidate molecule for anti-cancer or anti-metastatic therapy in human can-cers [19,36,48,50,73,115,178]. Several targets for *FSCN1* are being developed and include miRNA, siRNA, shRNA, small molecule inhibitors, and nanobodies [73,91–97,99,140,150,179–189].

In multiple types of cancers, in vitro studies demonstrated that overexpression of miRNAs targeting *FSCN1* in cancer cell lines reduce cell growth, proliferation, migration, and invasion [91–95,97,99], thus indicating miRNAs or miRNA-based reagents as potential therapeutic options. On the other hand, siRNAs specifically degrade targeted mRNA; in vitro and in vivo studies reported *FSCN1* knockdown by siRNA leading to decreased cell migration and metastasis, respectively [54,73,140,150,182,183]. Over the last 10 years, more than 50 therapeutic RNAi-based drugs entered phase- I, II, and III trials, of which 15 phase- I, II, and III programs are dedicated to cancer treatment [190]. While miRNAs and siRNAs can be developed as therapeutics for metastatic cancers, there are several limi-tations in their role in clinical settings. Overcoming the key challenges, including adverse side-effects, delivery systems and administration paths, dosage concerns, and off-target effects, is necessary to develop RNAi-based therapies for cancer and other diseases [191]. Multiple immune-related side-effects and severe hyperbilirubinemia were some of the adverse events that developed during clinical trials of miRNA-based therapies [192–194]. Even though several preclinical studies use mouse models of cancer, only few miRNA candidates have reached clinical phases. Further investigations, including pharmokinetic studies in animal models, are essential to understand the role of RNAi-based therapies in humans [191]. On the other hand, nanotechnology aims to provide multipurpose plat-forms to allow safe biomolecule delivery, enhance therapeutic efficacy, reduce drug dosage, and minimize adverse events [195]. However, these systems are yet to reach human trial

phase as nanocarrier application is dependent on various parameters (average diameter, charge, shape, surface chemistry, and polydispersity index) [195]. In solid tumors, although nanoparticles are stabilized, their mechanistic entry is more complex plausibly due to the involvement of trans-endothelial pathways [196,197]. Moreover, establishing the optimal dose in RNAi-based therapy is complex as treating patients with either a non-active or potential toxic dose is unethical [191]. Since initial doses for phase I/II trials are derived from in vitro and in vivo data (preclinical), various variables including size, volume, immune response, administration routes, and toxicity are major areas of concern [191,198]. It is worth noting that, while RNAi-based therapy is frequently administered intravenously or subcutaneously, development of oral therapy is essential for clinical trials [199]. Finally, RNAi-based therapeutics come with a high cost to cover both RNAi-based products and emerging nanocarriers as compared to prevailing anti-cancer therapeutics; therefore, the cost–benefit ratio is another challenge involved in this kind of therapy [200].

Experiments using inhibitory nanobodies against FSCN1 protein showed disruption of the FSCN1/actin-bundling [187]. Although in vitro studies using FSCN1-specific nanobodies in breast (MDA-MB-231) and prostate (PC3) cancer cells inhibited the formation of invadopodium and cell invasion [187], the use of FSCN1-specific antibodies in clinical settings needs to be established. Moreover, series of thiazole derivatives, isoquinolone, and pyrazolo[4,3-c] pyridine were also reported to be potential inhibitors of metastasis by targeting FSCN1 [181,189].

Likewise, small molecule inhibitors can reduce tumor cell migration and invasion and help pave the way against *FSCN1*-induced tumors [75,179,184–186]. In ovarian cancer, Wang et al. treated the ovarian cancer cell line (ES-2) with a Leucine aminopeptidase 3 (LAP3) inhibitor, bestatin [188]. Bestatin was found to significantly inhibit tumor cell migration and invasion by blocking *FSCN1* promoter and reducing its expression, thus acting as a plausible anti-metastatic therapeutic agent [188]. Other studies have shown that migrastatin and its analogues target *FSCN1* and block its activity, thereby reducing cell migration, invasion, and tumor metastasis [179,185]. In addition to migrastatin, another investigation in colorectal cancer cells showed an antimigratory and anti-invasive effect of imipramine (anti-depressant) by inhibiting *FSCN1* activity [75], thus introducing a novel molecular targeted treatment in *FSCN1*-induced tumors. A novel small molecule compound G2 and its derived analogs (NP-G2-011, NP-G2-036, NP-G2-044, and NP-G2-050) were tested and displayed anti-metastatic properties along with enhanced response and survival in in vivo models by blocking *FSCN1* activity [184,186]. Recently, the phase 1A clinical trial in ovarian cancer patients was carried out to evaluate the dosage and safety of NP-G2-044; the drug was administered daily as a single oral dose (200–2100 mg) for 6 weeks, including four weeks of daily dosing and two weeks rest period [180]. While no dose-limiting toxicity and fatality were reported, the trial demonstrated the inhibitor (NP-G2-044) as a safe single-drug, with a daily dose of 1600 mg as the provisional recommended phase 2 dose [180]. Prior to treatment with the drug (NP-G2-044), ovarian cancer patients with metastasis to visceral organs were treated with anti-cancer therapeutic drugs. Treatment with NP-G2-044 showed a comparitavely better treatment efficacy as compared to treatment with anti-cancer therapeutic modalities [180]. Moreover, the drug displayed anti-tumor and anti-metastatic properties including progression-free-survival and metastasis-free interval, particularly for metastatic ovarian cancer patients [180]. Proposed future studies include a phase 2A clinical trial to assess the efficacy of NP-G2-044 at the identified dose (1600 mg), both in monotherapy as well as in combination with anti-PD-(L)1 immune checkpoint inhibitors [180]. Table 2 summarizes anti-fascin-based therapeutic approaches.

Since *FSCN1* can stimulate cancer cell migration and metastasis, there are several limitations in developing therapeutic targets against *FSCN1*. While *FSCN1* is not expressed in adult epithelial tissues, it is normally expressed in other adult non-epithelial tissues [14], raising the concern that *FSCN1* inhibitors may have negative side effects. Specifically, the inhibition of *FSCN1* may cause neuronal, kidney, endocrine, wound healing, and immune defects.

Table 2. Anti-fascin-based Therapeutic Approaches.

Therapeutic Approach	Outcome	Reference
FASNb5 (Fascin nanobody, Kd~35 nM, 1:1 stoichiometry)	Invadopodium instability	[187]
CORNb2 (Cortactin nanobody, Kd~75 nM, 1:1 stoichiometry)	Blocks invadopodium precursor formation and MMP secretion	[187]
Migrastatin and its analogues	Inhibits cell migration, invasion, and metastasis	[179,185]
Thiazole derivatives	Inhibits cell migration and suppresses angiogenesis	[189]
Bestatin (LAP3 inhibitor)	Inhibits FSCN1 expression and suppresses tumor cell migration and invasion in a dose-dependent manner	[188]
Isoquinolone and pyrazolo[4,3-c]pyridine inhibitors	Disrupts actin binding	[181]
G2 compound	Inhibits actin structures, migration, and invasion of cancer cells	[186]
NP-G2-044	Increase in duration of treatment, progression-free-survival, and metastasis-free interval. Displays anti-tumor and anti-metastatic activity	[180,184]
NP-G2-044 and PD-L1 inhibitor	In progress	[180]
Curcumin	Blocks fascin expression through JAK/STAT3 pathway downregulation. Inhibits cell attachment, invasion, and migration	[149]

7. Conclusions

FSCN1 is regulated by several signaling pathways (AMPK/mTOR, Wnt/β-catenin, and MAPK) and is overexpressed in various human carcinomas including gynecological cancers; however, understanding the exact molecular mechanisms underlying *FSCN1* deregulation and interaction with other genes and oncoviruses, especially in gynecological cancers, is still nascent. Although several studies have indicated a potential diagnostic utility of *FSCN1*, its therapeutic role as an anti-cancer target is still under investigation. We believe that further studies are needed, including the development of conditional transgenic and/or knockout animal models, to determine the role of *FSCN1* targeting as a potential therapeutic route for gynecological carcinomas.

Abbreviations

Abl: Tyrosine-protein kinase ABL1; ABS: actin-binding site; AhR: aryl hydrocarbon receptor; ALCL: Anaplastic large cell lymphoma; ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; AMPK: 5' adenosine monophosphate-activated protein

kinase; Cdc: Cell division control protein 42 homolog; CHL: Classical Hodgkin lymphoma; CREB: cAMP-response element binding protein; DLBCL: Diffuse large B-cell lymphoma; EBV: Epstein-Barr virus; EGF: Epidermal growth factor; EGFR: Epidermal growth factor receptor EMT: Epithelial-mesenchymal transition; ERK: Extracellular regulated kinase; FSCN: Fascin; GSK-3β: Glycogen Synthase Kinase-3 Beta; GTP: Guanosine triphosphate; HIF-1α: Hypoxia-inducible factor-1-alpha; HPV: Human papillomavirus; HTLV-1: human T-lymphotropic virus type-1; IHC: Immunohistochemistry; IL: Interleukin; JNK: c-Jun N-terminal kinase; kDa: Kilo Dalton; LAP3: Leucine aminopeptidase 3; LMP: Latent membrane protein; MAPK: Mitogen-activated protein kinase; miRNA: microRNA; MMP: Matrix metalloproteinase; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor kappa light chain enhancer of activated B cells; NT2: NTERA-2; Rac1: Ras-related C3 botulinum toxin substrate 1; SCID: Severe combined immunodeficiency; Ser: Serine; shRNA: Small hairpin RNA; siRNA: Small interfering RNA; SMAD4: SMAD family member 4, Mothers against decapentaplegic homolog 4; SNAI2: Snail Family Transcriptional Repressor 2; SNAIL: Zinc finger protein SNAI1; Sp1: Specificity protein 1; Src: Proto-oncogene tyrosine-protein kinase sarcoma; STAT3: Signal transducer and activator of transcription 3; TCF: T-cell factor; TEAD: Transcriptional enhanced associate domain; TFs: Transcription factors; TMA: Tissue microarray; TNF: Tumor necrosis factor; UTR: Untranslated region; Wnt: Wingless; YAP: Yes-associated protein.

References

1. Edwards, R.A.; Bryan, J. Fascins, a family of actin bundling proteins. *Cell Motil.* **1995**, *32*, 1–9. [CrossRef]
2. Bryan, J.; Edwards, R.; Matsudaira, P.; Otto, J.; Wulfkuhle, J. Fascin, an echinoid actin-bundling protein, is a homolog of the Drosophila singed gene product. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 9115–9119. [CrossRef] [PubMed]
3. Holthuis, J.C.; Schoonderwoert, V.T.; Martens, G.J. A vertebrate homolog of the actin-bundling protein fascin. *Biochim. Biophys. Acta* **1994**, *1219*, 184–188. [CrossRef]
4. Edwards, R.A.; Herrera-Sosa, H.; Otto, J.; Bryan, J. Cloning and expression of a murine fascin homolog from mouse brain. *J. Biol. Chem.* **1995**, *270*, 10764–10770. [CrossRef] [PubMed]
5. Vignjevic, D.; Kojima, S.; Aratyn, Y.; Danciu, O.; Svitkina, T.; Borisy, G.G. Role of fascin in filopodial protrusion. *J. Cell. Biol.* **2006**, *174*, 863–875. [CrossRef]
6. Elkhatib, N.; Neu, M.B.; Zensen, C.; Schmoller, K.M.; Louvard, D.; Bausch, A.R.; Betz, T.; Vignjevic, D.M. Fascin plays a role in stress fiber organization and focal adhesion disassembly. *Curr. Biol.* **2014**, *24*, 1492–1499. [CrossRef] [PubMed]
7. Li, A.; Dawson, J.C.; Forero-Vargas, M.; Spence, H.J.; Yu, X.; König, I.; Anderson, K.; Machesky, L.M. The actin-bundling protein fascin stabilizes actin in invadopodia and potentiates protrusive invasion. *Curr. Biol.* **2010**, *20*, 339–345. [CrossRef] [PubMed]
8. Adams, J.C. Characterization of cell-matrix adhesion requirements for the formation of fascin microspikes. *Mol. Biol. Cell.* **1997**, *8*, 2345–2363. [CrossRef] [PubMed]
9. Adams, J.C. Roles of fascin in cell adhesion and motility. *Curr. Opin. Cell Biol.* **2004**, *16*, 590–596. [CrossRef]
10. Jayo, A.; Parsons, M. Fascin: A key regulator of cytoskeletal dynamics. *Int. J. Biochem. Cell Biol.* **2010**, *42*, 1614–1617. [CrossRef]
11. Adams, J.C. Fascin protrusions in cell interactions. *Trends Cardiovasc. Med.* **2004**, *14*, 221–226. [CrossRef] [PubMed]
12. Villari, G.; Jayo, A.; Zanet, J.; Fitch, B.; Serrels, B.; Frame, M.; Stramer, B.M.; Goult, B.T.; Parsons, M. A direct interaction between fascin and microtubules contributes to adhesion dynamics and cell migration. *J. Cell Sci.* **2015**, *128*, 4601–4614. [CrossRef] [PubMed]
13. Saad, A.; Bijian, K.; Qiu, D.; da Silva, S.D.; Marques, M.; Chang, C.H.; Nassour, H.; Ramotar, D.; Damaraju, S.; Mackey, J.; et al. Insights into a novel nuclear function for Fascin in the regulation of the amino-acid transporter SLC3A2. *Sci. Rep.* **2016**, *6*, 36699. [CrossRef]
14. De Arcangelis, A.; Georges-Labouesse, E.; Adams, J.C. Expression of fascin-1, the gene encoding the actin-bundling protein fascin-1, during mouse embryogenesis. *Gene Expr. Patterns* **2004**, *4*, 637–643. [CrossRef] [PubMed]
15. Perrin, B.J.; Strandjord, D.M.; Narayanan, P.; Henderson, D.M.; Johnson, K.R.; Ervasti, J.M. β-Actin and fascin-2 cooperate to maintain stereocilia length. *J. Neurosci.* **2013**, *33*, 8114–8121. [CrossRef]
16. Lin-Jones, J.; Burnside, B. Retina-specific protein fascin 2 is an actin cross-linker associated with actin bundles in photoreceptor inner segments and calycal processes. *Investig. Ophthalmol. Vis. Sci.* **2007**, *48*, 1380–1388. [CrossRef]
17. Tubb, B.; Mulholland, D.J.; Vogl, W.; Lan, Z.J.; Niederberger, C.; Cooney, A.; Bryan, J. Testis fascin (FSCN3): A novel paralog of the actin-bundling protein fascin expressed specifically in the elongate spermatid head. *Exp. Cell Res.* **2002**, *275*, 92–109. [CrossRef]
18. Zhang, F.R.; Tao, L.H.; Shen, Z.Y.; Lv, Z.; Xu, L.Y.; Li, E.M. Fascin expression in human embryonic, fetal, and normal adult tissue. *J. Histochem. Cytochem.* **2008**, *56*, 193–199. [CrossRef]
19. Ma, Y.; Machesky, L.M. Fascin1 in carcinomas: Its regulation and prognostic value. *Int J. Cancer* **2015**, *137*, 2534–2544. [CrossRef]

20. Sedeh, R.S.; Fedorov, A.A.; Fedorov, E.V.; Ono, S.; Matsumura, F.; Almo, S.C.; Bathe, M. Structure, evolutionary conservation, and conformational dynamics of Homo sapiens fascin-1, an F-actin crosslinking protein. *J. Mol. Biol.* **2010**, *400*, 589–604. [CrossRef]

21. Yang, S.; Huang, F.K.; Huang, J.; Chen, S.; Jakoncic, J.; Leo-Macias, A.; Diaz-Avalos, R.; Chen, L.; Zhang, J.J.; Huang, X.Y. Molecular mechanism of fascin function in filopodial formation. *J. Biol. Chem.* **2013**, *288*, 274–284. [CrossRef] [PubMed]

22. Ono, S.; Yamakita, Y.; Yamashiro, S.; Matsudaira, P.T.; Gnarra, J.R.; Obinata, T.; Matsumura, F. Identification of an actin binding region and a protein kinase C phosphorylation site on human fascin. *J. Biol. Chem.* **1997**, *272*, 2527–2533. [CrossRef] [PubMed]

23. Anilkumar, N.; Parsons, M.; Monk, R.; Ng, T.; Adams, J.C. Interaction of fascin and protein kinase Calpha: A novel intersection in cell adhesion and motility. *EMBO J.* **2003**, *22*, 5390–5402. [CrossRef] [PubMed]

24. Jansen, S.; Collins, A.; Yang, C.; Rebowski, G.; Svitkina, T.; Dominguez, R. Mechanism of actin filament bundling by fascin. *J. Biol. Chem.* **2011**, *286*, 30087–30096. [CrossRef]

25. Zanet, J.; Jayo, A.; Plaza, S.; Millard, T.; Parsons, M.; Stramer, B. Fascin promotes filopodia formation independent of its role in actin bundling. *J. Cell Biol.* **2012**, *197*, 477–486. [CrossRef]

26. Lin, S.; Lu, S.; Mulaj, M.; Fang, B.; Keeley, T.; Wan, L.; Hao, J.; Muschol, M.; Sun, J.; Yang, S. Monoubiquitination Inhibits the Actin Bundling Activity of Fascin. *J. Biol. Chem.* **2016**, *291*, 27323–27333. [CrossRef]

27. Wang, H.R.; Zhang, Y.; Ozdamar, B.; Ogunjimi, A.A.; Alexandrova, E.; Thomsen, G.H.; Wrana, J.L. Regulation of cell polarity and protrusion formation by targeting RhoA for degradation. *Science* **2003**, *302*, 1775–1779. [CrossRef] [PubMed]

28. Yamakita, Y.; Matsumura, F.; Yamashiro, S. Fascin1 is dispensable for mouse development but is favorable for neonatal survival. *Cell Motil Cytoskelet.* **2009**, *66*, 524–534. [CrossRef]

29. Ross, R.; Jonuleit, H.; Bros, M.; Ross, X.L.; Yamashiro, S.; Matsumura, F.; Enk, A.H.; Knop, J.; Reske-Kunz, A.B. Expression of the actin-bundling protein fascin in cultured human dendritic cells correlates with dendritic morphology and cell differentiation. *J. Invest. Derm.* **2000**, *115*, 658–663. [CrossRef]

30. Yamakita, Y.; Matsumura, F.; Lipscomb, M.W.; Chou, P.C.; Werlen, G.; Burkhardt, J.K.; Yamashiro, S. Fascin1 promotes cell migration of mature dendritic cells. *J. Immunol.* **2011**, *186*, 2850–2859. [CrossRef]

31. Jayo, A.; Malboubi, M.; Antoku, S.; Chang, W.; Ortiz-Zapater, E.; Groen, C.; Pfisterer, K.; Tootle, T.; Charras, G.; Gundersen, G.G.; et al. Fascin Regulates Nuclear Movement and Deformation in Migrating Cells. *Dev. Cell* **2016**, *38*, 371–383. [CrossRef]

32. Beghein, E.; Devriese, D.; Van Hoey, E.; Gettemans, J. Cortactin and fascin-1 regulate extracellular vesicle release by controlling endosomal trafficking or invadopodia formation and function. *Sci. Rep.* **2018**, *8*, 15606. [CrossRef] [PubMed]

33. Lamb, M.C.; Anliker, K.K.; Tootle, T.L. Fascin regulates protrusions and delamination to mediate invasive, collective cell migration in vivo. *Dev. Dyn.* **2020**, *249*, 961–982. [CrossRef] [PubMed]

34. Mosialos, G.; Birkenbach, M.; Ayehunie, S.; Matsumura, F.; Pinkus, G.S.; Kieff, E.; Langhoff, E. Circulating human dendritic cells differentially express high levels of a 55-kd actin-bundling protein. *Am. J. Pathol.* **1996**, *148*, 593–600.

35. Boer, E.F.; Howell, E.D.; Schilling, T.F.; Jette, C.A.; Stewart, R.A. Fascin1-dependent Filopodia are required for directional migration of a subset of neural crest cells. *PLoS Genet.* **2015**, *11*, e1004946. [CrossRef] [PubMed]

36. Hashimoto, Y.; Skacel, M.; Adams, J.C. Roles of fascin in human carcinoma motility and signaling: Prospects for a novel biomarker? *Int. J. Biochem. Cell Biol.* **2005**, *37*, 1787–1804. [CrossRef]

37. Li, J.; Zhang, S.; Pei, M.; Wu, L.; Liu, Y.; Li, H.; Lu, J.; Li, X. FSCN1 Promotes Epithelial-Mesenchymal Transition Through Increasing Snail1 in Ovarian Cancer Cells. *Cell Physiol. Biochem.* **2018**, *49*, 1766–1777. [CrossRef] [PubMed]

38. Gonzalez-Reyes, C.; Marcial-Medina, C.; Cervantes-Anaya, N.; Cortes-Reynosa, P.; Salazar, E.P. Migration and invasion induced by linoleic acid are mediated through fascin in MDA-MB-231 breast cancer cells. *Mol. Cell Biochem.* **2018**, *443*, 1–10. [CrossRef] [PubMed]

39. Jawhari, A.U.; Buda, A.; Jenkins, M.; Shehzad, K.; Sarraf, C.; Noda, M.; Farthing, M.J.; Pignatelli, M.; Adams, J.C. Fascin, an actin-bundling protein, modulates colonic epithelial cell invasiveness and differentiation in vitro. *Am. J. Pathol.* **2003**, *162*, 69–80. [CrossRef]

40. Li, A.; Morton, J.P.; Ma, Y.; Karim, S.A.; Zhou, Y.; Faller, W.J.; Woodham, E.F.; Morris, H.T.; Stevenson, R.P.; Juin, A.; et al. Fascin is regulated by slug, promotes progression of pancreatic cancer in mice, and is associated with patient outcomes. *Gastroenterology* **2014**, *146*, 1386–1396.e1381–1317. [CrossRef]

41. Zhao, X.; Gao, S.; Ren, H.; Sun, W.; Zhang, H.; Sun, J.; Yang, S.; Hao, J. Hypoxia-inducible factor-1 promotes pancreatic ductal adenocarcinoma invasion and metastasis by activating transcription of the actin-bundling protein fascin. *Cancer Res.* **2014**, *74*, 2455–2464. [CrossRef] [PubMed]

42. Gunal, A.; Onguru, O.; Safali, M.; Beyzadeoglu, M. Fascin expression [corrected] in glial tumors and its prognostic significance in glioblastomas. *Neuropathology* **2008**, *28*, 382–386. [CrossRef] [PubMed]

43. Ma, Y.; Faller, W.J.; Sansom, O.J.; Brown, E.R.; Doig, T.N.; Melton, D.W.; Machesky, L.M. Fascin expression is increased in metastatic lesions but does not correlate with progression nor outcome in melanoma. *Melanoma Res.* **2015**, *25*, 169–172. [CrossRef]

44. Mohr, C.F.; Gross, C.; Bros, M.; Reske-Kunz, A.B.; Biesinger, B.; Thoma-Kress, A.K. Regulation of the tumor marker Fascin by the viral oncoprotein Tax of human T-cell leukemia virus type 1 (HTLV-1) depends on promoter activation and on a promoter-independent mechanism. *Virology* **2015**, *485*, 481–491. [CrossRef]

45. Idrees, R.; Ahmad, Z.; Qureshi, A.; Ahsan, A.; Pervez, S. Is fascin really a useful marker in distinguishing between classical Hodgkin's lymphoma and various types of non-Hodgkin's lymphomas in difficult cases? *J. Clin. Pathol.* **2010**, *63*, 571–574. [CrossRef] [PubMed]

46. Hou, J.; Guo, Z.Y.; Xie, J.J.; Li, E.M.; Xu, L.Y. Fascin overexpression is regulated by the transactivation of the promoter but not by its hypomethylation in esophageal squamous cell carcinoma. *Mol. Med. Rep.* **2009**, *2*, 843–849. [CrossRef]
47. Grothey, A.; Hashizume, R.; Sahin, A.A.; McCrea, P.D. Fascin, an actin-bundling protein associated with cell motility, is upregulated in hormone receptor negative breast cancer. *Br. J. Cancer* **2000**, *83*, 870–873. [CrossRef]
48. Tan, V.Y.; Lewis, S.J.; Adams, J.C.; Martin, R.M. Association of fascin-1 with mortality, disease progression and metastasis in carcinomas: A systematic review and meta-analysis. *BMC Med.* **2013**, *11*, 52. [CrossRef]
49. Kulasingam, V.; Diamandis, E.P. Fascin-1 is a novel biomarker of aggressiveness in some carcinomas. *BMC Med.* **2013**, *11*, 53. [CrossRef]
50. Gao, X.; Wu, D.H. Fascin expression in human epithelial tumors and its clinical significance. *Nan Fang Yi Ke Da Xue Xue Bao* **2008**, *28*, 953–955.
51. Xing, P.; Li, J.G.; Jin, F.; Zhao, T.T.; Liu, Q.; Dong, H.T.; Wei, X.L. Fascin, an actin-bundling protein, promotes breast cancer progression in vitro. *Cell Biochem. Funct.* **2011**, *29*, 303–310. [CrossRef]
52. Liang, Z.; Wang, Y.; Shen, Z.; Teng, X.; Li, X.; Li, C.; Wu, W.; Zhou, Z.; Wang, Z. Fascin 1 promoted the growth and migration of non-small cell lung cancer cells by activating YAP/TEAD signaling. *Tumour Biol.* **2016**, *37*, 10909–10915. [CrossRef]
53. Alam, H.; Bhate, A.V.; Gangadaran, P.; Sawant, S.S.; Salot, S.; Sehgal, L.; Dange, P.P.; Chaukar, D.A.; D'Cruz, A.K.; Kannanl, S.; et al. Fascin overexpression promotes neoplastic progression in oral squamous cell carcinoma. *BMC Cancer* **2012**, *12*, 32. [CrossRef]
54. Lin, S.; Huang, C.; Gunda, V.; Sun, J.; Chellappan, S.P.; Li, Z.; Izumi, V.; Fang, B.; Koomen, J.; Singh, P.K.; et al. Fascin Controls Metastatic Colonization and Mitochondrial Oxidative Phosphorylation by Remodeling Mitochondrial Actin Filaments. *Cell Rep.* **2019**, *28*, 2824–2836.e2828. [CrossRef]
55. Bi, J.; Zhu, Y.; Chen, X.; Yu, M.; Zhang, Y.; Li, B.; Sun, J.; Shen, H.; Kong, C. The Role of Fascin in Migration and Invasion of Urothelial Carcinoma of the Bladder. *Urol. Int.* **2013**, *91*, 227–235. [CrossRef]
56. Al-Alwan, M.; Olabi, S.; Ghebeh, H.; Barhoush, E.; Tulbah, A.; Al-Tweigeri, T.; Ajarim, D.; Adra, C. Fascin is a key regulator of breast cancer invasion that acts via the modification of metastasis-associated molecules. *PLoS ONE* **2011**, *6*, e27339. [CrossRef] [PubMed]
57. Heinz, L.S.; Muhs, S.; Schiewek, J.; Grüb, S.; Nalaskowski, M.; Lin, Y.N.; Wikman, H.; Oliveira-Ferrer, L.; Lange, T.; Wellbrock, J.; et al. Strong fascin expression promotes metastasis independent of its F-actin bundling activity. *Oncotarget* **2017**, *8*, 110077–110091. [CrossRef] [PubMed]
58. Zhao, J.; Zhou, Y.; Zhang, Z.; Tian, F.; Ma, N.; Liu, T.; Gu, Z.; Wang, Y. Upregulated fascin1 in non-small cell lung cancer promotes the migration and invasiveness, but not proliferation. *Cancer Lett.* **2010**, *290*, 238–247. [CrossRef] [PubMed]
59. Zhao, D.; Zhang, T.; Hou, X.M.; Ling, X.L. Knockdown of fascin-1 expression suppresses cell migration and invasion of non-small cell lung cancer by regulating the MAPK pathway. *Biochem. Biophys. Res. Commun.* **2018**, *497*, 694–699. [CrossRef]
60. Parker, A.L.; Kavallaris, M.; McCarroll, J.A. Microtubules and their role in cellular stress in cancer. *Front. Oncol.* **2014**, *4*, 153. [CrossRef]
61. Lombardi, M.L.; Jaalouk, D.E.; Shanahan, C.M.; Burke, B.; Roux, K.J.; Lammerding, J. The interaction between nesprins and sun proteins at the nuclear envelope is critical for force transmission between the nucleus and cytoskeleton. *J. Biol. Chem.* **2011**, *286*, 26743–26753. [CrossRef] [PubMed]
62. Harada, T.; Swift, J.; Irianto, J.; Shin, J.W.; Spinler, K.R.; Athirasala, A.; Diegmiller, R.; Dingal, P.C.; Ivanovska, I.L.; Discher, D.E. Nuclear lamin stiffness is a barrier to 3D migration, but softness can limit survival. *J. Cell Biol.* **2014**, *204*, 669–682. [CrossRef] [PubMed]
63. Groen, C.M.; Jayo, A.; Parsons, M.; Tootle, T.L. Prostaglandins regulate nuclear localization of Fascin and its function in nucleolar architecture. *Mol. Biol. Cell* **2015**, *26*, 1901–1917. [CrossRef]
64. Kelpsch, D.J.; Groen, C.M.; Fagan, T.N.; Sudhir, S.; Tootle, T.L. Fascin regulates nuclear actin during Drosophila oogenesis. *Mol. Biol. Cell* **2016**, *27*, 2965–2979. [CrossRef] [PubMed]
65. Fiore, A.; Spencer, V.A.; Mori, H.; Carvalho, H.F.; Bissell, M.J.; Bruni-Cardoso, A. Laminin-111 and the Level of Nuclear Actin Regulate Epithelial Quiescence via Exportin-6. *Cell Rep.* **2017**, *19*, 2102–2115. [CrossRef]
66. Hein, N.; Hannan, K.M.; George, A.J.; Sanij, E.; Hannan, R.D. The nucleolus: An emerging target for cancer therapy. *Trends Mol. Med.* **2013**, *19*, 643–654. [CrossRef]
67. Quin, J.E.; Devlin, J.R.; Cameron, D.; Hannan, K.M.; Pearson, R.B.; Hannan, R.D. Targeting the nucleolus for cancer intervention. *Biochim. Biophys. Acta* **2014**, *1842*, 802–816. [CrossRef]
68. Mao, X.; Duan, X.; Jiang, B. Fascin Induces Epithelial-Mesenchymal Transition of Cholangiocarcinoma Cells by Regulating Wnt/β-Catenin Signaling. *Med. Sci. Monit.* **2016**, *22*, 3479–3485. [CrossRef]
69. Bu, M.; Liu, X.; Liu, X.; Xu, W. Upregulation of fascin-1 is involved in HIF-1α-dependent invasion and migration of hypopharyngeal squamous cell carcinoma. *Int. J. Oncol.* **2019**, *55*, 488–498. [CrossRef]
70. Arlt, M.J.; Kuzmanov, A.; Snedeker, J.G.; Fuchs, B.; Silvan, U.; Sabile, A.A. Fascin-1 enhances experimental osteosarcoma tumor formation and metastasis and is related to poor patient outcome. *BMC Cancer* **2019**, *19*, 83. [CrossRef]
71. Minn, A.J.; Gupta, G.P.; Siegel, P.M.; Bos, P.D.; Shu, W.; Giri, D.D.; Viale, A.; Olshen, A.B.; Gerald, W.L.; Massagué, J. Genes that mediate breast cancer metastasis to lung. *Nature* **2005**, *436*, 518–524. [CrossRef]

72. Schoumacher, M.; El-Marjou, F.; Laé, M.; Kambou, N.; Louvard, D.; Robine, S.; Vignjevic, D.M. Conditional expression of fascin increases tumor progression in a mouse model of intestinal cancer. *Eur. J. Cell Biol.* **2014**, *93*, 388–395. [CrossRef] [PubMed]

73. Darnel, A.D.; Behmoaram, E.; Vollmer, R.T.; Corcos, J.; Bijian, K.; Sircar, K.; Su, J.; Jiao, J.; Alaoui-Jamali, M.A.; Bismar, T.A. Fascin regulates prostate cancer cell invasion and is associated with metastasis and biochemical failure in prostate cancer. *Clin. Cancer Res.* **2009**, *15*, 1376–1383. [CrossRef] [PubMed]

74. Zhang, M.; Zhao, Z.; Duan, X.; Chen, P.; Peng, Z.; Qiu, H. FSCN1 predicts survival and is regulated by a PI3K-dependent mechanism in renal cell carcinoma. *J. Cell Physiol.* **2018**, *233*, 4748–4758. [CrossRef]

75. Alburquerque-González, B.; Bernabé-García, M.; Montoro-García, S.; Bernabé-García, Á.; Rodrigues, P.C.; Ruiz Sanz, J.; López-Calderón, F.F.; Luque, I.; Nicolas, F.J.; Cayuela, M.L.; et al. New role of the antidepressant imipramine as a Fascin1 inhibitor in colorectal cancer cells. *Exp. Mol. Med.* **2020**, *52*, 281–292. [CrossRef]

76. Lin, S.; Taylor, M.D.; Singh, P.K.; Yang, S. How does fascin promote cancer metastasis? *FEBS J.* **2021**, *288*, 1434–1446. [CrossRef] [PubMed]

77. Hashimoto, Y.; Loftis, D.W.; Adams, J.C. Fascin-1 promoter activity is regulated by CREB and the aryl hydrocarbon receptor in human carcinoma cells. *PLoS ONE* **2009**, *4*, e5130. [CrossRef]

78. Lee, M.K.; Park, J.H.; Gi, S.H.; Hwang, Y.S. IL-1β Induces Fascin Expression and Increases Cancer Invasion. *Anticancer Res.* **2018**, *38*, 6127–6132. [CrossRef]

79. Snyder, M.; Huang, X.-Y.; Zhang, J.J. Signal transducers and activators of transcription 3 (STAT3) directly regulates cytokine-induced fascin expression and is required for breast cancer cell migration. *J. Biol. Chem.* **2011**, *286*, 38886–38893. [CrossRef]

80. Snyder, M.; Huang, J.; Huang, X.Y.; Zhang, J.J. A signal transducer and activator of transcription 3·Nuclear Factor κB (Stat3·NFκB) complex is necessary for the expression of fascin in metastatic breast cancer cells in response to interleukin (IL)-6 and tumor necrosis factor (TNF)-α. *J. Biol. Chem.* **2014**, *289*, 30082–30089. [CrossRef]

81. Yao, J.; Qian, C.-J.; Ye, B.; Zhao, Z.-Q.; Wei, J.; Liang, Y.; Zhang, X. Signal transducer and activator of transcription 3 signaling upregulates fascin via nuclear factor-κB in gastric cancer: Implications in cell invasion and migration. *Oncol. Lett.* **2014**, *7*, 902–908. [CrossRef]

82. Yang, Y.; Zhao, Q.; Cai, Z.; Cheng, G.; Chen, M.; Wang, J.; Zhong, H. Fas Signaling Promotes Gastric Cancer Metastasis through STAT3-Dependent Upregulation of Fascin. *PLoS ONE* **2015**, *10*, e0125132. [CrossRef]

83. Kim, S.J.; Choi, I.J.; Cheong, T.C.; Lee, S.J.; Lotan, R.; Park, S.H.; Chun, K.H. Galectin-3 increases gastric cancer cell motility by up-regulating fascin-1 expression. *Gastroenterology* **2010**, *138*, 1035–1045.e1031–1032. [CrossRef]

84. Vignjevic, D.; Schoumacher, M.; Gavert, N.; Janssen, K.P.; Jih, G.; Laé, M.; Louvard, D.; Ben-Ze'ev, A.; Robine, S. Fascin, a novel target of beta-catenin-TCF signaling, is expressed at the invasive front of human colon cancer. *Cancer Res.* **2007**, *67*, 6844–6853. [CrossRef] [PubMed]

85. Grothey, A.; Hashizume, R.; Ji, H.; Tubb, B.E.; Patrick, C.W., Jr.; Yu, D.; Mooney, E.E.; McCrea, P.D. C-erbB-2/ HER-2 upregulates fascin, an actin-bundling protein associated with cell motility, in human breast cancer cell lines. *Oncogene* **2000**, *19*, 4864–4875. [CrossRef]

86. Sui, X.; Zhu, J.; Tang, H.; Wang, C.; Zhou, J.; Han, W.; Wang, X.; Fang, Y.; Xu, Y.; Li, D.; et al. p53 controls colorectal cancer cell invasion by inhibiting the NF-κB-mediated activation of Fascin. *Oncotarget* **2015**, *6*, 22869–22879. [CrossRef]

87. Lu, X.F.; Li, E.M.; Du, Z.P.; Xie, J.J.; Guo, Z.Y.; Gao, S.Y.; Liao, L.D.; Shen, Z.Y.; Xie, D.; Xu, L.Y. Specificity protein 1 regulates fascin expression in esophageal squamous cell carcinoma as the result of the epidermal growth factor/extracellular signal-regulated kinase signaling pathway activation. *Cell Mol. Life Sci.* **2010**, *67*, 3313–3329. [CrossRef] [PubMed]

88. Wang, L.; Jia, Y.; Jiang, Z.; Gao, W.; Wang, B. FSCN1 is upregulated by SNAI2 and promotes epithelial to mesenchymal transition in head and neck squamous cell carcinoma. *Cell Biol. Int.* **2017**, *41*, 833–841. [CrossRef]

89. Megiorni, F.; Indovina, P.; Mora, B.; Mazzilli, M.C. Minor expression of fascin-1 gene (FSCN1) in NTera2 cells depleted of CREB-binding protein. *Neurosci. Lett* **2005**, *381*, 169–174. [CrossRef] [PubMed]

90. Wang, G.; Zhu, S.; Gu, Y.; Chen, Q.; Liu, X.; Fu, H. MicroRNA-145 and MicroRNA-133a Inhibited Proliferation, Migration, and Invasion, While Promoted Apoptosis in Hepatocellular Carcinoma Cells Via Targeting FSCN1. *Dig. Dis. Sci.* **2015**, *60*, 3044–3052. [CrossRef]

91. Feng, Y.; Zhu, J.; Ou, C.; Deng, Z.; Chen, M.; Huang, W.; Li, L. MicroRNA-145 inhibits tumour growth and metastasis in colorectal cancer by targeting fascin-1. *Br. J. Cancer* **2014**, *110*, 2300–2309. [CrossRef]

92. Li, Y.-Q.; He, Q.-M.; Ren, X.-Y.; Tang, X.-R.; Xu, Y.-F.; Wen, X.; Yang, X.-J.; Ma, J.; Liu, N. MiR-145 Inhibits Metastasis by Targeting Fascin Actin-Bundling Protein 1 in Nasopharyngeal Carcinoma. *PLoS ONE* **2015**, *10*, e0122228. [CrossRef] [PubMed]

93. Gao, W.; Zhang, C.; Li, W.; Li, H.; Sang, J.; Zhao, Q.; Bo, Y.; Luo, H.; Zheng, X.; Lu, Y.; et al. Promoter Methylation-Regulated miR-145-5p Inhibits Laryngeal Squamous Cell Carcinoma Progression by Targeting FSCN1. *Mol. Ther.* **2019**, *27*, 365–379. [CrossRef] [PubMed]

94. Kano, M.; Seki, N.; Kikkawa, N.; Fujimura, L.; Hoshino, I.; Akutsu, Y.; Chiyomaru, T.; Enokida, H.; Nakagawa, M.; Matsubara, H. miR-145, miR-133a and miR-133b: Tumor-suppressive miRNAs target FSCN1 in esophageal squamous cell carcinoma. *Int. J. Cancer* **2010**, *127*, 2804–2814. [CrossRef]

95. Li, Y.-Q.; Lu, J.-H.; Bao, X.-M.; Wang, X.-F.; Wu, J.-H.; Hong, W.-Q. MiR-24 functions as a tumor suppressor in nasopharyngeal carcinoma through targeting FSCN1. *J. Exp. Clin. Cancer Res.* **2015**, *34*, 130. [CrossRef]

96.　Wu, Z.-s.; Wang, C.-q.; Xiang, R.; Liu, X.; Ye, S.; Yang, X.-q.; Zhang, G.-h.; Xu, X.-c.; Zhu, T.; Wu, Q. Loss of miR-133a expression associated with poor survival of breast cancer and restoration of miR-133a expression inhibited breast cancer cell growth and invasion. *BMC Cancer* **2012**, *12*, 51. [CrossRef] [PubMed]

97.　Zhao, H.; Kang, X.; Xia, X.; Wo, L.; Gu, X.; Hu, Y.; Xie, X.; Chang, H.; Lou, L.; Shen, X. miR-145 suppresses breast cancer cell migration by targeting FSCN-1 and inhibiting epithelial-mesenchymal transition. *Am. J. Transl. Res.* **2016**, *8*, 3106–3114.

98.　Chen, J.-J.; Cai, W.-Y.; Liu, X.-W.; Luo, Q.-C.; Chen, G.; Huang, W.-F.; Li, N.; Cai, J.-C. Reverse Correlation between MicroRNA-145 and FSCN1 Affecting Gastric Cancer Migration and Invasion. *PLoS ONE* **2015**, *10*, e0126890. [CrossRef]

99.　Ma, L.; Li, L.L. miR-145 Contributes to the Progression of Cervical Carcinoma by Directly Regulating FSCN1. *Cell Transpl.* **2019**, *28*, 1299–1305. [CrossRef]

100.　Qin, Y.; Dang, X.; Li, W.; Ma, Q. miR-133a functions as a tumor suppressor and directly targets FSCN1 in pancreatic cancer. *Oncol Res.* **2013**, *21*, 353–363. [CrossRef]

101.　Xue, M.; Zhao, L.; Yang, F.; Li, Z.; Li, G. MicroRNA-145 inhibits the malignant phenotypes of gastric carcinoma cells via downregulation of fascin 1 expression. *Mol. Med. Rep.* **2016**, *13*, 1033–1039. [CrossRef] [PubMed]

102.　Li, X.; Han, X.; Wei, P.; Yang, J.; Sun, J. Knockdown of lncRNA CCAT1 enhances sensitivity of paclitaxel in prostate cancer via regulating miR-24-3p and FSCN1. *Cancer Biol.* **2020**, *21*, 452–462. [CrossRef] [PubMed]

103.　Liu, R.; Liao, J.; Yang, M.; Sheng, J.; Yang, H.; Wang, Y.; Pan, E.; Guo, W.; Pu, Y.; Kim, S.J.; et al. The Cluster of miR-143 and miR-145 Affects the Risk for Esophageal Squamous Cell Carcinoma through Co-Regulating Fascin Homolog 1. *PLoS ONE* **2012**, *7*, e33987. [CrossRef] [PubMed]

104.　Zhang, N.; Nan, A.; Chen, L.; Li, X.; Jia, Y.; Qiu, M.; Dai, X.; Zhou, H.; Zhu, J.; Zhang, H.; et al. Circular RNA circSATB2 promotes progression of non-small cell lung cancer cells. *Mol. Cancer* **2020**, *19*, 101. [CrossRef]

105.　Li, Y.; Gao, Y.; Xu, Y.; Ma, H.; Yang, M. Down-regulation of miR-326 is associated with poor prognosis and promotes growth and metastasis by targeting FSCN1 in gastric cancer. *Growth Factors* **2015**, *33*, 267–274. [CrossRef]

106.　Yu, S.; Xie, H.; Zhang, J.; Wang, D.; Song, Y.; Zhang, S.; Zheng, S.; Wang, J. MicroRNA-663 suppresses the proliferation and invasion of colorectal cancer cells by directly targeting FSCN1. *Mol. Med. Rep.* **2017**, *16*, 9707–9714. [CrossRef]

107.　Chen, M.B.; Wei, M.X.; Han, J.Y.; Wu, X.Y.; Li, C.; Wang, J.; Shen, W.; Lu, P.H. MicroRNA-451 regulates AMPK/mTORC1 signaling and fascin1 expression in HT-29 colorectal cancer. *Cell Signal.* **2014**, *26*, 102–109. [CrossRef]

108.　Mosialos, G.; Yamashiro, S.; Baughman, R.W.; Matsudaira, P.; Vara, L.; Matsumura, F.; Kieff, E.; Birkenbach, M. Epstein-Barr virus infection induces expression in B lymphocytes of a novel gene encoding an evolutionarily conserved 55-kilodalton actin-bundling protein. *J. Virol.* **1994**, *68*, 7320–7328. [CrossRef]

109.　Küppers, R. B cells under influence: Transformation of B cells by Epstein-Barr virus. *Nat. Rev. Immunol.* **2003**, *3*, 801–812. [CrossRef]

110.　Liu, Q.Y.; Han, A.J.; You, S.Y.; Dong, Y.; Yang, Q.X.; Wu, J.H.; Li, M.F. Correlation of Epstein-Barr virus-encoded latent membrane protein 1 (LMP1) to fascin and phosphorylated Stat3 in nasopharyngeal carcinoma. *Ai Zheng* **2008**, *27*, 1070–1076.

111.　Ahsan, N.; Kanda, T.; Nagashima, K.; Takada, K. Epstein-Barr virus transforming protein LMP1 plays a critical role in virus production. *J. Virol.* **2005**, *79*, 4415–4424. [CrossRef] [PubMed]

112.　Nanbo, A.; Terada, H.; Kachi, K.; Takada, K.; Matsuda, T. Roles of cell signaling pathways in cell-to-cell contact-mediated Epstein-Barr virus transmission. *J. Virol.* **2012**, *86*, 9285–9296. [CrossRef] [PubMed]

113.　Mohr, C.F.; Kalmer, M.; Gross, C.; Mann, M.C.; Sterz, K.R.; Kieser, A.; Fleckenstein, B.; Kress, A.K. The tumor marker Fascin is induced by the Epstein-Barr virus-encoded oncoprotein LMP1 via NF-κB in lymphocytes and contributes to their invasive migration. *Cell Commun. Signal.* **2014**, *12*, 46. [CrossRef] [PubMed]

114.　Endo, K.; Kondo, S.; Shackleford, J.; Horikawa, T.; Kitagawa, N.; Yoshizaki, T.; Furukawa, M.; Zen, Y.; Pagano, J.S. Phosphorylated ezrin is associated with EBV latent membrane protein 1 in nasopharyngeal carcinoma and induces cell migration. *Oncogene* **2009**, *28*, 1725–1735. [CrossRef]

115.　Al-Antary, N.; Farghaly, H.; Aboulkassim, T.; Yasmeen, A.; Akil, N.; Al Moustafa, A.-E. Epstein-Barr virus and its association with Fascin expression in colorectal cancers in the Syrian population: A tissue microarray study. *Hum. Vaccin Immunother.* **2017**, *13*, 1573–1578. [CrossRef]

116.　Son, B.K.; Kim, D.H.; Min, K.W.; Kim, E.K.; Kwon, M.J. Smad4/Fascin index is highly prognostic in patients with diffuse type EBV-associated gastric cancer. *Pathol. Res. Pr.* **2018**, *214*, 475–481. [CrossRef]

117.　Kress, A.K.; Kalmer, M.; Rowan, A.G.; Grassmann, R.; Fleckenstein, B. The tumor marker Fascin is strongly induced by the Tax oncoprotein of HTLV-1 through NF-kappaB signals. *Blood* **2011**, *117*, 3609–3612. [CrossRef] [PubMed]

118.　Karube, K.; Takatori, M.; Sakihama, S.; Tsuruta, Y.; Miyagi, T.; Morichika, K.; Kitamura, S.; Nakada, N.; Hayashi, M.; Tomori, S.; et al. Clinicopathological features of adult T-cell leukemia/lymphoma with HTLV-1-infected Hodgkin and Reed-Sternberg-like cells. *Blood Adv.* **2021**, *5*, 198–206. [CrossRef]

119.　Gross, C.; Wiesmann, V.; Millen, S.; Kalmer, M.; Wittenberg, T.; Gettemans, J.; Thoma-Kress, A.K. The Tax-Inducible Actin-Bundling Protein Fascin Is Crucial for Release and Cell-to-Cell Transmission of Human T-Cell Leukemia Virus Type 1 (HTLV-1). *PLoS Pathog.* **2016**, *12*, e1005916. [CrossRef]

120.　Graflund, M.; Sorbe, B.; Sigurdardóttir, S.; Karlsson, M. HPV-DNA, vascular space invasion, and their impact on the clinical outcome in early-stage cervical carcinomas. *Int J. Gynecol. Cancer* **2004**, *14*, 896–902. [CrossRef]

121. Smith, J.S.; Lindsay, L.; Hoots, B.; Keys, J.; Franceschi, S.; Winer, R.; Clifford, G.M. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: A meta-analysis update. *Int J. Cancer* **2007**, *121*, 621–632. [CrossRef]

122. Yasmeen, A.; Alachkar, A.; Dekhil, H.; Gambacorti-Passerini, C.; Al Moustafa, A.-E. Locking Src/Abl Tyrosine Kinase Activities Regulate Cell Differentiation and Invasion of Human Cervical Cancer Cells Expressing E6/E7 Oncoproteins of High-Risk HPV. *J. Oncol.* **2010**, *2010*, 530130. [CrossRef]

123. Yousefi Ghalejoogh, Z.; Mirakhor Samani, S.; Shatizadeh Malekshahi, S.; Shahsiah, R.; Yavarian, J.; KianI, S.J. Human papilloma virus infection and fascin over-expression in squamous cell carcinoma of the cervix. *Med. J. Islam. Repub. Iran.* **2018**, *32*, 134. [CrossRef]

124. Ghabreau, L.; Segal, E.; Yasmeen, A.; Kassab, A.; Akil, N.; Al Moustafa, A.-E. High-risk human papillomavirus infections in colorectal cancer in the Syrian population and their association with Fascin, Id-1 and P-cadherin expressions: A tissue microarray study. *Clin. Cancer Investig. J.* **2012**, *1*, 26–30. [CrossRef]

125. Alici, O.; Kefeli, M.; Yildiz, L.; Baris, S.; Karagoz, F.; Kandemir, B. Fascin and EMMPRIN expression in primary mucinous tumors of ovary: A tissue microarray study. *Pathol. Res. Pract.* **2014**, *210*, 934–938. [CrossRef] [PubMed]

126. Cao, D.; Ji, H.; Ronnett, B.M. Expression of mesothelin, fascin, and prostate stem cell antigen in primary ovarian mucinous tumors and their utility in differentiating primary ovarian mucinous tumors from metastatic pancreatic mucinous carcinomas in the ovary. *Int J. Gynecol. Pathol.* **2005**, *24*, 67–72.

127. Daponte, A.; Kostopoulou, E.; Papandreou, C.N.; Daliani, D.D.; Minas, M.; Koukoulis, G.; Messinis, I.E. Prognostic significance of fascin expression in advanced poorly differentiated serous ovarian cancer. *Anticancer. Res.* **2008**, *28*, 1905–1910.

128. El-Balat, A.; Arsenic, R.; Sänger, N.; Karn, T.; Becker, S.; Holtrich, U.; Engels, K. Fascin-1 expression as stratification marker in borderline epithelial tumours of the ovary. *J. Clin. Pathol.* **2016**, *69*, 142–148. [CrossRef] [PubMed]

129. Gun, B.D.; Bahadir, B.; Bektas, S.; Barut, F.; Yurdakan, G.; Kandemir, N.O.; Ozdamar, S.O. Clinicopathological significance of fascin and CD44v6 expression in endometrioid carcinoma. *Diagn. Pathol.* **2012**, *7*, 80. [CrossRef] [PubMed]

130. Hanker, L.C.; Karn, T.; Holtrich, U.; Graeser, M.; Becker, S.; Reinhard, J.; Ruckhäberle, E.; Gevensleben, H.; Rody, A. Prognostic Impact of Fascin-1 (FSCN1) in Epithelial Ovarian Cancer. *Anticancer. Res.* **2013**, *33*, 371–377.

131. Hu, W.; McCrea, P.D.; Deavers, M.; Kavanagh, J.J.; Kudelka, A.P.; Verschraegen, C.F. Increased expression of fascin, motility associated protein, in cell cultures derived from ovarian cancer and in borderline and carcinomatous ovarian tumors. *Clin. Exp. Metastasis* **2000**, *18*, 83–88. [CrossRef] [PubMed]

132. Kabukcuoglu, S.; Oner, U.; Ozalp, S.S.; Bildirici, K.; Yalcin, O.T.; Colak, E. The role of actin bundling protein fascin in the progression of ovarian neoplasms. *Eur. J. Gynaecol. Oncol.* **2006**, *27*, 171–176.

133. Kabukcuoglu, S.; Oner, U.; Ozalp, S.S.; Dundar, E.; Yalcin, O.T.; Colak, E. Prognostic significance of fascin expression in endometrioid carcinoma. *Eur. J. Gynaecol. Oncol.* **2006**, *27*, 481–486. [PubMed]

134. Kabukcuoglu, S.; Ozalp, S.S.; Oner, U.; Bildirici, K.; Yalcin, O.T.; Oge, T.; Colak, E. Actin bundling protein fascin expression in ovarian neoplasms: Comparison of histopathologic features of tumors obtained by the first and secondary cytoreduction surgeries. *Eur. J. Gynaecol. Oncol.* **2006**, *27*, 123–128.

135. Kefeli, M.; Yildiz, L.; Kaya, F.C.; Aydin, O.; Kandemir, B. Fascin expression in uterine smooth muscle tumors. *Int J. Gynecol. Pathol.* **2009**, *28*, 328–333. [CrossRef] [PubMed]

136. Koay, M.H.; Crook, M.; Stewart, C.J. Fascin expression in cervical normal squamous epithelium, cervical intraepithelial neoplasia, and superficially invasive (stage IA1) squamous carcinoma of the cervix. *Pathology* **2014**, *46*, 433–438. [CrossRef]

137. Kostopoulou, E.; Daponte, A.; Terzis, A.; Nakou, M.; Chiotoglou, I.; Theodosiou, D.; Chatzichristodoulou, C.; Messinis, I.E.; Koukoulis, G. Fascin in ovarian epithelial tumors. *Histol. Histopathol.* **2008**, *23*, 935–944. [CrossRef]

138. Lin, C.K.; Chao, T.K.; Yu, C.P.; Yu, M.H.; Jin, J.S. The expression of six biomarkers in the four most common ovarian cancers: Correlation with clinicopathological parameters. *Apmis* **2009**, *117*, 162–175. [CrossRef]

139. Lin, C.K.; Su, H.Y.; Tsai, W.C.; Sheu, L.F.; Jin, J.S. Association of cortactin, fascin-1 and epidermal growth factor receptor (EGFR) expression in ovarian carcinomas: Correlation with clinicopathological parameters. *Dis. Markers.* **2008**, *25*, 17–26. [CrossRef]

140. McGuire, S.; Kara, B.; Hart, P.C.; Montag, A.; Wroblewski, K.; Fazal, S.; Huang, X.Y.; Lengyel, E.; Kenny, H.A. Inhibition of fascin in cancer and stromal cells blocks ovarian cancer metastasis. *Gynecol. Oncol.* **2019**, *153*, 405–415. [CrossRef]

141. Onder, S.; Taskin, O.C.; Sen, F.; Topuz, S.; Kucucuk, S.; Sozen, H.; Ilhan, R.; Tuzlali, S.; Yavuz, E. High expression of SALL4 and fascin, and loss of E-cadherin expression in undifferentiated/dedifferentiated carcinomas of the endometrium: An immunohisto-chemical and clinicopathologic study. *Medicine* **2017**, *96*, e6248. [CrossRef] [PubMed]

142. Richmond, A.M.; Blake, E.A.; Torkko, K.; Smith, E.E.; Spillman, M.A.; Post, M.D. Fascin Is Associated With Aggressive Behavior and Poor Outcome in Uterine Carcinosarcoma. *Int. J. Gynecol. Cancer* **2017**, *27*, 1895–1903. [CrossRef]

143. Stewart, C.J.; Crook, M.L. Fascin expression in undifferentiated and dedifferentiated endometrial carcinoma. *Hum. Pathol.* **2015**, *46*, 1514–1520. [CrossRef] [PubMed]

144. Stewart, C.J.R.; Crook, M.; Loi, S. Fascin expression in endocervical neoplasia: Correlation with tumour morphology and growth pattern. *J. Clin. Pathol.* **2012**, *65*, 213–217. [CrossRef]

145. Stewart, C.J.R.; Crook, M.L. Fascin and cyclin D1 immunoreactivity in non-neoplastic vulvar squamous epithelium, vulvar intraepithelial neoplasia and invasive squamous carcinoma: Correlation with Ki67 and p16 protein expression. *J. Clin. Pathol.* **2014**, *67*, 319–325. [CrossRef] [PubMed]

146. Umehara, R.; Kurata, A.; Takanashi, M.; Hashimoto, H.; Fujita, K.; Nagao, T.; Kuroda, M. Fascin as a Useful Marker for Identifying Neural Components in Immature Teratomas of Human Ovary and Those Derived From Murine Embryonic Stem Cells. *Int. J. Gynecol. Pathol.* **2019**, *38*, 377–385. [CrossRef]

147. Wen, Y.H.; Yee, H.; Goswami, S.; Shukla, P.S. Fascin expression in serous tumors of ovary correlates with aggressiveness of malignancy. *Int. J. Gynecol. Pathol.* **2009**, *28*, 187–192. [CrossRef]

148. Yoshihara, M.; Yamakita, Y.; Kajiyama, H.; Senga, T.; Koya, Y.; Yamashita, M.; Nawa, A.; Kikkawa, F. Filopodia play an important role in the trans-mesothelial migration of ovarian cancer cells. *Exp. Cell Res.* **2020**, *392*, 112011. [CrossRef]

149. Kim, M.J.; Park, K.-S.; Kim, K.-T.; Gil, E.Y. The inhibitory effect of curcumin via fascin suppression through JAK/STAT3 pathway on metastasis and recurrence of ovary cancer cells. *BMC Womens Health* **2020**, *20*, 256. [CrossRef]

150. Hashimoto, Y.; Parsons, M.; Adams, J.C. Dual actin-bundling and protein kinase C-binding activities of fascin regulate carcinoma cell migration downstream of Rac and contribute to metastasis. *Mol. Biol. Cell* **2007**, *18*, 4591–4602. [CrossRef]

151. Zaino, R.J. Unusual patterns of endometrial carcinoma including MELF and its relation to epithelial mesenchymal transition. *Int. J. Gynecol. Pathol.* **2014**, *33*, 357–364. [CrossRef]

152. Shen, T.Y.; Mei, L.L.; Qiu, Y.T.; Shi, Z.Z. Identification of candidate target genes of genomic aberrations in esophageal squamous cell carcinoma. *Oncol. Lett* **2016**, *12*, 2956–2961. [CrossRef] [PubMed]

153. Takikita, M.; Hu, N.; Shou, J.-Z.; Giffen, C.; Wang, Q.-H.; Wang, C.; Hewitt, S.M.; Taylor, P.R. Fascin and CK4 as Biomarkers for Esophageal Squamous Cell Carcinoma. *Anticancer Res.* **2011**, *31*, 945–952.

154. Zhang, H.; Xu, L.; Xiao, D.; Xie, J.; Zeng, H.; Cai, W.; Niu, Y.; Yang, Z.; Shen, Z.; Li, E. Fascin is a potential biomarker for early-stage oesophageal squamous cell carcinoma. *J. Clin. Pathol.* **2006**, *59*, 958–964. [CrossRef] [PubMed]

155. Hashimoto, Y.; Ito, T.; Inoue, H.; Okumura, T.; Tanaka, E.; Tsunoda, S.; Higashiyama, M.; Watanabe, G.; Imamura, M.; Shimada, Y. Prognostic Significance of Fascin Overexpression in Human Esophageal Squamous Cell Carcinoma. *Clin. Cancer Res.* **2005**, *11*, 2597–2605. [CrossRef] [PubMed]

156. Hsu, K.-F.; Lin, C.-K.; Yu, C.-P.; Tzao, C.; Lee, S.-C.; Lee, Y.-Y.; Tsai, W.-C.; Jin, J.-S. Cortactin, fascin, and survivin expression associated with clinicopathological parameters in esophageal squamous cell carcinoma. *Dis. Esophagus* **2009**, *22*, 402–408. [CrossRef] [PubMed]

157. Wang, G.; Gu, Y.; Lu, W.; Liu, X.; Fu, H. Fascin1 promotes gastric cancer progression by facilitatingcell migrationand epithelial-mesenchymal transition. *Pathol. Res. Pr.* **2018**, *214*, 1362–1369. [CrossRef]

158. Zheng, H.-C.; Zhao, S. The meta and bioinformatics analysis of fascin expression in gastric cancer: A potential marker for aggressiveness and worse prognosis. *Oncotarget* **2017**, *8*, 105574–105583. [CrossRef]

159. Li, X.; Zheng, H.; Hara, T.; Takahashi, H.; Masuda, S.; Wang, Z.; Yang, X.; Guan, Y.; Takano, Y. Aberrant expression of cortactin and fascin are effective markers for pathogenesis, invasion, metastasis and prognosis of gastric carcinomas. *Int. J. Oncol.* **2008**, *33*, 69–79. [CrossRef]

160. Hashimoto, Y.; Shimada, Y.; Kawamura, J.; Yamasaki, S.; Imamura, M. The Prognostic Relevance of Fascin Expression in Human Gastric Carcinoma. *Oncology* **2004**, *67*, 262–270. [CrossRef]

161. Tsai, W.C.; Jin, J.S.; Chang, W.K.; Chan, D.C.; Yeh, M.K.; Cherng, S.C.; Lin, L.F.; Sheu, L.F.; Chao, Y.C. Association of cortactin and fascin-1 expression in gastric adenocarcinoma: Correlation with clinicopathological parameters. *J. Histochem. Cytochem.* **2007**, *55*, 955–962. [CrossRef] [PubMed]

162. Tu, L.; Xu, J.; Wang, M.; Zhao, W.Y.; Zhang, Z.Z.; Zhu, C.C.; Tang, D.F.; Zhang, Y.Q.; Wang, D.H.; Zuo, J.; et al. Correlations of fascin-1 and cadherin-17 protein expression with clinicopathologic features and prognosis of patients with gastric cancer. *Tumour. Biol.* **2016**, *37*, 8775–8782. [CrossRef] [PubMed]

163. Kim, S.J.; Kim, D.C.; Kim, M.C.; Jung, G.J.; Kim, K.H.; Jang, J.S.; Kwon, H.C.; Kim, Y.M.; Jeong, J.S. Fascin expression is related to poor survival in gastric cancer. *Pathol. Int.* **2012**, *62*, 777–784. [CrossRef] [PubMed]

164. Wang, C.-Q.; Wang, Y.; Huang, B.-F.; Tang, C.-H.; Du, Z.; Zeng, Y.; Wang, Q.; Shao, J.-K.; Jin, L.-L. High Expression of Both Resistin and Fascin-1 Predicts a Poor Prognosis in Patients with Colorectal Cancer. *BioMed Res. Int.* **2020**, *2020*, 8753175. [CrossRef] [PubMed]

165. Hashimoto, Y.; Skacel, M.; Lavery, I.C.; Mukherjee, A.L.; Casey, G.; Adams, J.C. Prognostic significance of fascin expression in advanced colorectal cancer: An immunohistochemical study of colorectal adenomas and adenocarcinomas. *BMC Cancer* **2006**, *6*, 241. [CrossRef]

166. Tsai, W.C.; Chao, Y.C.; Sheu, L.F.; Chang, J.L.; Nieh, S.; Jin, J.S. Overexpression of fascin-1 in advanced colorectal adenocarcinoma: Tissue microarray analysis of immunostaining scores with clinicopathological parameters. *Dis. Markers* **2007**, *23*, 153–160. [CrossRef]

167. Ozerhan, I.H.; Ersoz, N.; Onguru, O.; Ozturk, M.; Kurt, B.; Cetiner, S. Fascin expression in colorectal carcinomas. *Clinics* **2010**, *65*, 157–164. [CrossRef]

168. Oh, S.Y.; Kim, Y.B.; Suh, K.W.; Paek, O.J.; Moon, H.Y. Prognostic impact of fascin-1 expression is more significant in advanced colorectal cancer. *J. Surg. Res.* **2012**, *172*, 102–108. [CrossRef]

169. Koçer, N.E.; Kayaselçuk, F. Is availability of anti-EGFR therapy for the colorectal adenocarcinomas showing fascin expression limited? *Target. Oncol.* **2014**, *9*, 171–175. [CrossRef]

170. Iguchi, T.; Aishima, S.; Umeda, K.; Sanefuji, K.; Fujita, N.; Sugimachi, K.; Gion, T.; Taketomi, A.; Maehara, Y.; Tsuneyoshi, M. Fascin expression in progression and prognosis of hepatocellular carcinoma. *J. Surg. Oncol.* **2009**, *100*, 575–579. [CrossRef]

171. Lin, C.K.; Jin, J.S.; Yu, C.P.; Tsai, W.C. Expression of LGR8 and related biomarkers in hepatocellular carcinoma: Correlation with clinicopathological parameters. *Chin. J. Physiol.* **2011**, *54*, 161–168. [CrossRef] [PubMed]

172. Hayashi, Y.; Osanai, M.; Lee, G.-H. Fascin-1 expression correlates with repression of E-cadherin expression in hepatocellular carcinoma cells and augments their invasiveness in combination with matrix metalloproteinases. *Cancer Sci.* **2011**, *102*, 1228–1235. [CrossRef]

173. Yamaguchi, H.; Inoue, T.; Eguchi, T.; Miyasaka, Y.; Ohuchida, K.; Mizumoto, K.; Yamada, T.; Yamaguchi, K.; Tanaka, M.; Tsuneyoshi, M. Fascin overexpression in intraductal papillary mucinous neoplasms (adenomas, borderline neoplasms, and carcinomas) of the pancreas, correlated with increased histological grade. *Mod. Pathol.* **2007**, *20*, 552–561. [CrossRef]

174. Pinkus, G.S.; Pinkus, J.L.; Langhoff, E.; Matsumura, F.; Yamashiro, S.; Mosialos, G.; Said, J.W. Fascin, a sensitive new marker for Reed-Sternberg cells of hodgkin's disease. Evidence for a dendritic or B cell derivation? *Am. J. Pathol.* **1997**, *150*, 543–562. [PubMed]

175. Kim, S.H.; Choe, J.Y.; Jeon, Y.; Huh, J.; Jung, H.R.; Choi, Y.D.; Kim, H.J.; Cha, H.J.; Park, W.S.; Kim, J.E. Frequent expression of follicular dendritic cell markers in Hodgkin lymphoma and anaplastic large cell lymphoma. *J. Clin. Pathol.* **2013**, *66*, 589–596. [CrossRef]

176. El Kramani, N.; Elsherbiny, N.M.; El-Gayar, A.M.; Ebrahim, M.A.; Al-Gayyar, M.M.H. Clinical significance of the TNF-α receptors, TNFRSF2 and TNFRSF9, on cell migration molecules Fascin-1 and Versican in acute leukemia. *Cytokine* **2018**, *111*, 523–529. [CrossRef] [PubMed]

177. Bakshi, N.A.; Finn, W.G.; Schnitzer, B.; Valdez, R.; Ross, C.W. Fascin expression in diffuse large B-cell lymphoma, anaplastic large cell lymphoma, and classical Hodgkin lymphoma. *Arch. Pathol. Lab. Med.* **2007**, *131*, 742–747. [CrossRef]

178. Lee, H.J.; An, H.J.; Kim, T.H.; Kim, G.; Kang, H.; Heo, J.H.; Kwon, A.-Y.; Kim, S. Fascin expression is inversely correlated with breast cancer metastasis suppressor 1 and predicts a worse survival outcome in node-negative breast cancer patients. *J. Cancer* **2017**, *8*, 3122–3129. [CrossRef]

179. Chen, L.; Yang, S.; Jakoncic, J.; Zhang, J.J.; Huang, X.-Y. Migrastatin analogues target fascin to block tumour metastasis. *Nature* **2010**, *464*, 1062–1066. [CrossRef]

180. Chung, V.; Jhaveri, K.L.; Hoff, D.D.V.; Huang, X.-Y.; Garmey, E.G.; Zhang, J.; Tsai, F.Y.-C. Phase 1A clinical trial of the first-in-class fascin inhibitor NP-G2-044 evaluating safety and anti-tumor activity in patients with advanced and metastatic solid tumors. *J. Clin. Oncol.* **2021**, *39*, 2548. [CrossRef]

181. Francis, S.; Croft, D.; Schüttelkopf, A.W.; Parry, C.; Pugliese, A.; Cameron, K.; Claydon, S.; Drysdale, M.; Gardner, C.; Gohlke, A.; et al. Structure-based design, synthesis and biological evaluation of a novel series of isoquinolone and pyrazolo[4,3-c]pyridine inhibitors of fascin 1 as potential anti-metastatic agents. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1023–1029. [CrossRef]

182. Fu, H.; Hu, Z.; Wen, J.; Wang, K.; Liu, Y. TGF-beta promotes invasion and metastasis of gastric cancer cells by increasing fascin1 expression via ERK and JNK signal pathways. *Acta Biochim. Biophys. Sin.* **2009**, *41*, 648–656. [CrossRef] [PubMed]

183. Fu, H.; Wen, J.-F.; Hu, Z.-L.; Luo, G.-Q.; Ren, H.-Z. Knockdown of fascin1 expression suppresses the proliferation and metastasis of gastric cancer cells. *Pathology* **2009**, *41*, 655–660. [CrossRef] [PubMed]

184. Han, S.; Huang, J.; Liu, B.; Xing, B.; Bordeleau, F.; Reinhart-King, C.A.; Li, W.; Zhang, J.J.; Huang, X.Y. Improving fascin inhibitors to block tumor cell migration and metastasis. *Mol. Oncol.* **2016**, *10*, 966–980. [CrossRef] [PubMed]

185. Huang, F.-K.; Han, S.; Xing, B.; Huang, J.; Liu, B.; Bordeleau, F.; Reinhart-King, C.A.; Zhang, J.J.; Huang, X.-Y. Targeted inhibition of fascin function blocks tumour invasion and metastatic colonization. *Nat. Commun.* **2015**, *6*, 7465. [CrossRef]

186. Montoro-García, S.; Alburquerque-González, B.; Bernabé-García, Á.; Bernabé-García, M.; Rodrigues, P.C.; den-Haan, H.; Luque, I.; Nicolás, F.J.; Pérez-Sánchez, H.; Cayuela, M.L.; et al. Novel anti-invasive properties of a Fascin1 inhibitor on colorectal cancer cells. *J. Mol. Med.* **2020**, *98*, 383–394. [CrossRef]

187. Van Audenhove, I.; Boucherie, C.; Pieters, L.; Zwaenepoel, O.; Vanloo, B.; Martens, E.; Verbrugge, C.; Hassanzadeh-Ghassabeh, G.; Vandekerckhove, J.; Cornelissen, M.; et al. Stratifying fascin and cortactin function in invadopodium formation using inhibitory nanobodies and targeted subcellular delocalization. *FASEB J.* **2014**, *28*, 1805–1818. [CrossRef] [PubMed]

188. Wang, X.; Shi, L.; Deng, Y.; Qu, M.; Mao, S.; Xu, L.; Xu, W.; Fang, C. Inhibition of leucine aminopeptidase 3 suppresses invasion of ovarian cancer cells through down-regulation of fascin and MMP-2/9. *Eur. J. Pharmacol.* **2015**, *768*, 116–122. [CrossRef]

189. Zheng, S.; Zhong, Q.; Xi, Y.; Mottamal, M.; Zhang, Q.; Schroeder, R.L.; Sridhar, J.; He, L.; McFerrin, H.; Wang, G. Modification and biological evaluation of thiazole derivatives as novel inhibitors of metastatic cancer cell migration and invasion. *J. Med. Chem.* **2014**, *57*, 6653–6667. [CrossRef]

190. Zhang, S.; Cheng, Z.; Wang, Y.; Han, T. The Risks of miRNA Therapeutics: In a Drug Target Perspective. *Drug Des. Dev.* **2021**, *15*, 721–733. [CrossRef]

191. Reda El Sayed, S.; Cristante, J.; Guyon, L.; Denis, J.; Chabre, O.; Cherradi, N. MicroRNA Therapeutics in Cancer: Current Advances and Challenges. *Cancers* **2021**, *13*, 2680. [CrossRef]

192. Lindow, M.; Kauppinen, S. Discovering the first microRNA-targeted drug. *J. Cell Biol.* **2012**, *199*, 407–412. [CrossRef] [PubMed]

193. van der Ree, M.H.; van der Meer, A.J.; van Nuenen, A.C.; de Bruijne, J.; Ottosen, S.; Janssen, H.L.; Kootstra, N.A.; Reesink, H.W. Miravirsen dosing in chronic hepatitis C patients results in decreased microRNA-122 levels without affecting other microRNAs in plasma. *Aliment. Pharm.* **2016**, *43*, 102–113. [CrossRef]

194. Beg, M.S.; Brenner, A.J.; Sachdev, J.; Borad, M.; Kang, Y.K.; Stoudemire, J.; Smith, S.; Bader, A.G.; Kim, S.; Hong, D.S. Phase I study of MRX34, a liposomal miR-34a mimic, administered twice weekly in patients with advanced solid tumors. *Invest. New Drugs* **2017**, *35*, 180–188. [CrossRef] [PubMed]

195. De Jong, W.H.; Borm, P.J. Drug delivery and nanoparticles:applications and hazards. *Int J. Nanomed.* **2008**, *3*, 133–149. [CrossRef]

196. Sindhwani, S.; Syed, A.M.; Ngai, J.; Kingston, B.R.; Maiorino, L.; Rothschild, J.; MacMillan, P.; Zhang, Y.; Rajesh, N.U.; Hoang, T.; et al. The entry of nanoparticles into solid tumours. *Nat. Mater.* **2020**, *19*, 566–575. [CrossRef] [PubMed]

197. Blanco, E.; Shen, H.; Ferrari, M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nat. Biotechnol.* **2015**, *33*, 941–951. [CrossRef]

198. Elmén, J.; Lindow, M.; Schütz, S.; Lawrence, M.; Petri, A.; Obad, S.; Lindholm, M.; Hedtjärn, M.; Hansen, H.F.; Berger, U.; et al. LNA-mediated microRNA silencing in non-human primates. *Nature* **2008**, *452*, 896–899. [CrossRef] [PubMed]

199. Haute, D.V.; Berlin, J.M. Challenges in realizing selectivity for nanoparticle biodistribution and clearance: Lessons from gold nanoparticles. *Ther. Deliv.* **2017**, *8*, 763–774. [CrossRef]

200. Hare, J.I.; Lammers, T.; Ashford, M.B.; Puri, S.; Storm, G.; Barry, S.T. Challenges and strategies in anti-cancer nanomedicine development: An industry perspective. *Adv. Drug Deliv. Rev.* **2017**, *108*, 25–38. [CrossRef]